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COLLECTION, PRESERVATION AND TRANSFUSION OF PLATELETS*

With Special Reference to the Factors Affecting the "Survival Rate" and the Clinical Effectiveness of Transfused Platelets

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RECENT developments in the therapy of certain types of cancer with growth-suppressing agents, which are usually myelotoxic, as well as the threat of mass exposure to ionizing radiation, have focused increasing attention on the problem of collection, preservation and transfusion of platelets. Thus, bleeding due to thrombocytopenia is one of the most significantly limiting factors in the chemotherapy of leukemia and lymphoma. It is theoretically possible that, if a drastic but temporary depression of abnormal cell production could be obtained by various chemotherapeutic agents even at the expense of severe bone-marrow injury, lengthy remissions would occur in certain types of leukemia. However, this would require not only red cells, which are readily available, but, even more important, platelets for the control of the bleeding induced by the extreme thrombocytopenia. Since temporary but severe thrombocytopenia is common in many reversible cases of radiation injury, the ready availability of platelets would also be of great practical significance in the case of mass exposure to ionizing radiation.

With these considerations in mind, it may be useful to review briefly the various technics available at present for the collection, preservation and administration of platelets; their therapeutic effect in thrombocytopenia; and the factors that influence their preservation in vitro and their survival in vivo. Platelets are rather unstable when they come in contact with traumatized areas or with such foreign surfaces as glass and metal. This contact, resulting in the lysis of some platelets, initiates the process of blood coagulation. When thrombin or, possibly, other clotting agents are thereby formed, more platelets are agglutinated and lysed, and this process continues until most of the platelets have been destroyed.[1] When blood is collected by ordinary blood-bank procedures, with but little regard for the physical nature of the surfaces to which platelets are exposed, their agglutination and destruction are considerable and continue until complete mixing of the blood with the anticoagulant solution interrupts the autocatalytic process of blood coagulation. The use of vacuum, which may produce foaming, causes additional platelet clumping at the blood-air interface. This explains why many platelets are lost at the time of collection of the blood by ordinary procedures as well as when the blood is administered to the recipient. Although thrombocytes are fairly stable in incoagulable blood and plasma for a few days, transfusions of bank blood fail to elevate perceptibly the platelet count of a thrombocytopenic recipient. In many cases, moreover, normal plasma contains a globulin that may further cause a temporary depression of the platelet count in the recipient.[2]

Several materials recently introduced confer on glass and metal certain properties similar to those of nonwettable, endothelial-like surfaces.[3] Some are particularly valuable for the coating of needles, such as Arquad 2-C (dicoco-dimethyl-ammonium chloride), others for the coating of metal surfaces, such as lacquer Silicone (Dri-Bake and Pan-Glaze) and Teflon fluid, and still others for the coating of glassware, such as Silicone (methyl-chloro-silane). Arquad 2-C and Silicone, both of which give a permanent, nonpyrogenic coating to metal and glassware respectively, have been successfully employed for the collection of blood without great loss of platelets, provided tubes of plastic, nonwettable material are used for the collection and administration of blood. Entirely plastic systems have recently become available. A newly introduced anticoagulant, Sequestrene-Na$_3$ (di-sodium ethylendiamino tetraacetate dihydrate) has been found to affect morphologic and functional prop-

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erties of platelets to a lesser degree than previously used calcium-complexing agents.[4] Irreversible agglutination of platelets, an accident that easily occurs during the separation and concentration of platelets, has been reduced considerably by the use of surface-active agents, such as Tween-80 and Triton WR-1339.[5] These agents are effective and, in the concentration used, apparently innocuous. Finally, some ion-exchange resins, like Dowex-50 and IRC-50 in the sodium cycle (with a few of the sodium sites replaced by calcium), have a great affinity for platelets and will trap them as the blood that flows through is decalcified and made incoagulable.[6] Platelets can subsequently be recovered, at least in part, by elution with sodium citrate or Sequestrene-Na_3. Other, more complicated and less practical methods consist in the use of falling film centrifuges and "slicers." As a result of these developments, loss of platelets during the collection and storage of blood has been diminished greatly

TABLE 1. *Isolation and Concentration of Platelets by a Centrifugation Method.**

Blood collected (by gravity) in 0.1 vol. of anticoagulant solution†

Centrifugation at 4°C. (1000 rpm for 15 minutes)

Separation of supernatant plasma

0.1 vol. of 2 per cent Triton WR-1339 solution added

Centrifugation at 4°C. (1000 rpm for 10 minutes)

Platelet-rich plasma, relatively free of erythrocytes and leukocytes

Centrifugation at 4°C. (3000 rpm for 20 minutes)‡

Platelet-free supernatant plasma removed

Saline solution containing 0.1 vol. of 2 per cent solution of Triton WR-1339 added in volume equal to half the plasma originally collected

Centrifugation at 4°C. (3000 rpm for 20 minutes)

Packed platelets resuspended in saline solution or in other solution, added in volume equal to ⅓ of the plasma originally collected

Final platelet preparation

*The final yield of platelets can be increased by the use of polycythemic blood or several pints of normal blood.

†Sequestrene-Na_3 1 per cent in 0.7 per cent NaCl.

‡This step may be repeated if the sedimentation of platelets is not complete.

and platelets can now be isolated and concentrated without excessive destruction or injury to their physiologic properties. The most common available methods for administration of platelets are as follows. Direct transfusion of polycythemic (preferably) or normal blood with Silicone-coated syringes and Arquad 2-C-coated needles. Administration of polycythemic (preferably) or normal blood, collected by gravity into plastic bags containing ACD (acid citrate dextrose) solution or other anticoagulant, through plastic tubing. Administration, through plastic tubing, of platelet-rich plasma obtained by low-speed centrifugation. The blood is collected by gravity in plastic bags or Silicone-coated containers using sodium citrate (3.8 per cent), ACD solution or 1 per cent Sequestrene-Na_3 solution as anticoagulant (fully compatible donors should be selected). Spontaneous sedimentation and separation of red and white blood cells after addition of plasma volume expanders (dextran, glutamyl-peptide and so forth) to whole blood similarly collected may be utilized. Platelets remain in the supernatant plasma, which is separated and administered (fully compatible donors should be selected). Administration of concentrated platelets, isolated by multiple low-speed centrifugations, with or without preliminary use of plasma-volume expanders, and resuspended in small volume of their own plasma, in saline or other isotonic preservative solutions, with the help of surface-active agents (Tween 80, Triton WR-1339) to prevent their irreversible agglutination. Administration of platelets collected on ion-exchange-resin columns and subsequently eluted from them with the use of metal complexing agents (sodium citrate, Sequestrene-Na_3). Differential centrifugation is used in practically all separation methods, with the exception of the resin-column technic. This seems to offer the advantage of collecting platelets as a by-product during the collection of blood, leaving the rest of the cellular and plasmatic constituents available for administration or further separation. It has, however, the disadvantage of a low recovery (30 per cent, at least in our experience, as opposed to 70 and 80 per cent with most methods based on differential centrifugation). By the use of polycythemic donors[7, 8] or concentrating in small volume the platelets from several units of blood, it has become possible to administer large concentrations of platelets, and to analyze the resultant effects. In particular, it has been possible to investigate the effect of the platelets on the hemostatic mechanism of thrombocytopenic patients and the various factors that affect their survival and their physiologic activity in the recipient.

During the past three years, we have given platelet transfusions by at least three different methods: administration of polycythemic blood or plasma directly, with the use of multiple Silicone-coated syringes[7, 8]; transfusion of blood or plasma from polycythemic donors, collected in and administered by plastic sets or Silicone-coated glass bottles and plastic tubing, ACD solution or 1 per cent Sequestrene-Na_3 being employed as anticoagulants; administration of concentrates of platelets, isolated according to the technic described in Table 1. The procedure for the preparation of these concentrates is similar to that described by Minor and Burnett,[9] with one important difference: the original separation of platelet-rich plasma is accomplished by low-speed centrifugation of whole blood collected by gravity in Silicone-coated glassware and with Sequestrene-Na_3, as the anticoagulant. When compared to the method of Minor and Burnett,[5] our procedure yields a larger number of platelets, probably owing to the use of Silicone-coated surfaces.

Our studies have been conducted thus far on 83 patients for a total of 216 platelet transfusions without serious accidents. The patients transfused were as follows: idiopathic thrombocytopenic purpura, 45 cases (including 20 acute and 24 chronic and 1 associated with lupus erythematosus); "amegakaryocytic" secondary thrombocytopenic purpura, 33 cases (including 20 of acute leukemia, 6 of hypoplastic anemia, 5 of aplastic anemia, 1 of x-ray overdosage and 1 associated with triethylene-melamine therapy); and "hypersplenic" thrombocytopenic purpura, 5 cases (including 2 of "hypersplenism," 1 of Gaucher's disease and 2 of cirrhosis of the liver with portal hypertension). Together with studies in vivo, observations have been made on the preservation of platelets in vitro, as indicated by their ability to correct the coagulation defect and the deficient clot retraction of native human platelet-poor plasma.* Complete separation of plasma through centrifugation influences the preservation of the physiologic activity of platelets in vitro. Platelets suspended in their own plasma or resuspended in it after centrifugation at high speed are still able to normalize the clot retraction of platelet-poor native plasma after ten days' storage at 5°C. Their staining properties are unmodified, and, as indicated by other investigators,[9] their oxygen consumption is normal. If protected from bacterial contamination, these platelets normalize the clotting time and the utilization of prothrombin during clotting of platelet-poor native plasma for as long as six months after collection, apparently because this property is due to highly stable constituents of platelets. Platelets isolated in saline or other solutions, on the other hand, although still able to normalize the clotting time and the prothrombin utilization of platelet-poor plasma, have apparently lost staining properties after a few days and, in ten to twenty-four hours, the ability to restore the clot retraction of platelet-poor plasma. Data of other investigators[9] show that oxygen consumption ceases between thirty-six and seventy-two hours.

Even more pronounced are the detrimental effects of manipulation on the survival of platelets in vivo. When platelets are administered as platelet-rich polycythemic blood by direct transfusion into patients with secondary "amegakaryocytic" thrombocytopenic purpura (as in aplastic anemia), who were never previously transfused, they remain in the circulation between ninety-six and a hundred and twenty hours, and even longer in individual cases. The length of survival depends in large measure on the immediate elevation of the platelet count induced by the transfusion and, therefore, on the number of platelets successfully transfused. When a comparable number of platelets administered or collected with various technics are transfused into such patients with secondary thrombocytopenic purpura, the results are as shown in Figure 1. The longest survival is obtained with platelet-rich polycythemic blood transfused directly and then with polycythemic blood collected in Silicone-coated bottles or plastic bags. Much shorter "survival times" are obtained when platelets are separated and resuspended in their own plasma;

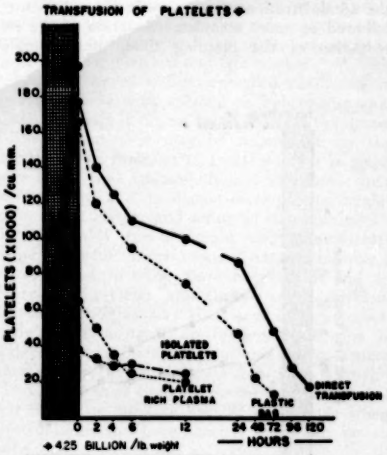

FIGURE 1. *"Survival Time" of Variously Treated Platelets Administered to Patients with Secondary, "Amegakaryocytic" Thrombocytopenic Purpura.*

finally, practically no elevation of the platelet count follows the administration of platelets isolated and resuspended in saline solution. It is probable that platelets subjected to many centrifugations and resuspensions are more easily disposed of by the body. The mechanism of this disposal is not clear at present, although we have noticed that the rate of disappearance of isolated and saline-resuspended platelets is delayed when they are transfused into a patient who has recently been splenectomized (Fig. 2).

Transfusions of platelets prepared in various ways are indicated for the control of bleeding in a number of conditions in which the hemorrhagic manifestations are due to quantitative or qualitative platelet deficiency. These include idiopathic thrombocytopenic purpura (slightly beneficial); secondary "amegakaryocytic" thrombocytopenic purpura (be-

*Native human platelet-poor plasma is obtained as follows: Silicone-coated glassware and Arquad 2-C coated needles are used in every step of the procedure; blood is collected and centrifuged at 4000 revolutions per minute for an hour. The supernatant plasma is separated and exhibits a complex hemostatic defect, possibly owing to the deficiency of many single constituents of the platelets. When transferred to glass test tubes in water bath at 37° C., this plasma clots only after several hours; it fails to show any clot retraction, and its serum, an hour after final completion of clotting, exhibits high prothrombin activity.

fore the development of resistance and platelet agglutinins); thrombocytoasthenias; before and during surgery in all patients with thrombocytopenia or thrombocytoasthenia; and for control of bleeding manifestations in thrombocytopenia due to myelosuppressive agents given during the treatment of leukemias and lymphomas. In all cases the combined use of platelet transfusions and ACTH (and, to a lesser degree, cortisone) affects favorably the vascular factor of hemostasis, which may be abnormal in many of the conditions listed above, both as a result of and independently of the existing thrombocytopenia. As previously reported,[7, 8] the administration of platelets in these patients is followed by more complete retraction of the clot, reduction of the bleeding time, more complete

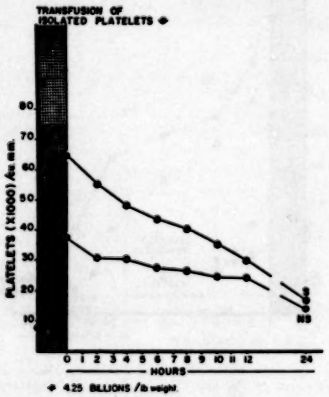

FIGURE 2. *"Survival Time" of Isolated Platelets Administered to a Patient with Aplastic Anemia before (Lower Curve) and after (Upper Curve) Splenectomy. The interval between experiments was two weeks.*

utilization of prothrombin during clotting and improvement of the capillary fragility and of the bleeding manifestations (Fig. 3). In all cases these effects ordinarily outlast the disappearance of the injected platelets from the circulation, but there is still a much more pronounced beneficial effect on the bleeding manifestations when platelet-rich polycythemic blood or plasma is used than when isolated platelets are administered. These observations suggest two conclusions: better and less traumatizing methods of platelet isolation, which will not affect the platelet "survival rate" in vivo, are still to be developed; and the hemostatic effect of platelets must be due, at least in part, to certain relatively stable constituents of platelets that are liberated when these bodies disintegrate.[10] This would explain why isolated platelets, which disappear rapidly from the circulation, may still exercise a beneficial effect on the bleeding manifestations of thrombocytopenia. It may be anticipated that, in the future, individual components of platelets with a specific role in the hemostatic mechanism will become available for clinical use.

The survival of platelets in vivo is affected even more strikingly by various pathologic states in the recipient. These include severe transfusion reactions and severe, uncontrolled bleeding, both of which also limit the value of platelet transfusions for correction of the hemostatic defects and the bleeding manifestations of thrombocytopenic patients. The platelet survival time is shortened considerably in the presence of platelet-destructive mechanisms due to idiopathic thrombocytopenic purpura, thrombocytopenia of drug sensitivity when the offending agent is still present in the circulation — otherwise,

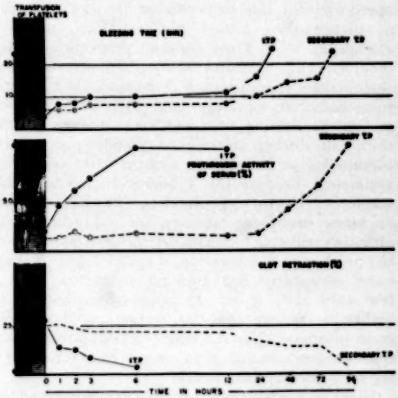

FIGURE 3. *Effect of the Administration of Platelets on the Hemostatic Mechanism of Patients with Idiopathic (I.T.P.) and Secondary (T.P.) Thrombocytopenic Purpura (Bleeding Time, Clot Retraction and Utilization of Prothrombin during Clotting).*

the "survival rate" is normal). Short survival times are also present in thrombotic thrombocytopenic purpura and with the development of acquired platelet agglutinins as a response to multiple transfusions of platelets or of platelet products. Some of these responses are nonspecific, whereas others suggest that a platelet-destructive mechanism is specifically involved. The presence of splenomegaly, irrespective of its etiology, may also cause fast disappearance of platelets. This is extremely rapid in patients with

idiopathic thrombocytopenic purpura, when even the direct transfusion of platelet-rich polycythemic blood may fail to elevate the platelet count of the recipient for more than a few minutes or a few hours (Fig. 4). The survival time is shorter in the acute than in the chronic types of idiopathic thrombocytopenic purpura, being roughly in relation to the platelet count of the patient studied. Although platelets disappear very rapidly in idiopathic thrombocytopenic purpura, their transfusion is still beneficial beyond the actual time of survival of platelets (Fig. 3). *In patients with this disease requiring splenectomy, platelet transfusions have allowed practically bloodless surgery.*

The short survival time of platelets in idiopathic thrombocytopenic purpura represents, thus far,

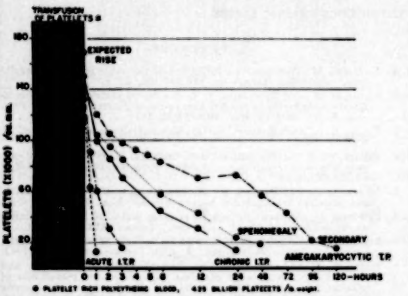

FIGURE 4. *"Survival Time" of Platelets Administered as Platelet-Rich Polycythemic Blood by Direct Transfusion to Patients with Various Forms of Thrombocytopenia.*

the only consistent evidence indicating that a platelet-destructive mechanism is responsible for the thrombocytopenia of some cases of the disease. Different pathogenetic mechanisms may be operative from case to case. We know little of the etiology of the acute variety and but little more of the etiology of the chronic type. Thus, in about 50 per cent of the chronic cases, destruction of platelets may be due to the presence of circulating platelet agglutinins. These are apparently able to cause immediate clumping of platelets in vitro, and to induce marked degenerative changes of the megakaryocytes, leading to defective platelet formation.[11, 12] Such alterations may be observed when the patient's plasma is injected into normal recipients. It is unfortunate that platelet agglutinins* are as yet detectable in only approximately 50 per cent of the cases of chronic idiopathic thrombocytopenic purpura. This may be due to inadequacy of the technics employed for their demonstration or even to fundamental differences from case to case. Although platelet agglutinins have many properties in common with known antibodies, their exact relation to platelet antigens has yet to be determined.* The relation of the spleen to these agglucinins is also quite uncertain, although it may remove from the circulation the platelets that have been damaged by the agglutinins.[12]

There is another significant limitation in the use of platelet transfusions for the management of the thrombocytopenic states. As patients with secondary or "amegakaryocytic" thrombocytopenia receive increasing numbers of platelet transfusions, the platelet survival time becomes progressively shorter. Moreover, the bleeding manifestations are no longer controllable and the clinical response to transfusion becomes less and less marked.[13, 14] This has been observed under controlled conditions in several patients with aplastic or hypoplastic anemia.[14] Although it cannot be denied that the course of the disease itself may be responsible for the changes in the response to transfusion, it is much more likely that isoimmunization develops, since we have been able to demonstrate platelet agglutinins in the plasma and serum of these patients.[14] This also holds true but more rarely for patients receiving multiple transfusions of bank blood over a limited period, in whom thrombocytopenia and resistance to platelet transfusions may develop. Platelet agglutinins may also occur in these cases, slowly disappearing if no further transfusion is received. When platelet agglutinins are no longer demonstrable, the platelet count returns to normal.[14]

In view of their complex chemical structure and their ability to produce specific antiserums when injected in heterologous species, there can be no doubt that platelets are antigenic, and so, in all

*Several technics for the detection of platelet agglutinins have been developed in this laboratory, as outlined in previous communications.[9, 10, 12] The following has been finally adopted for its merits of simplicity and reproducibility. (Silicone-coated glassware and Arquad 2-6 coated needles are used in all steps and procedures.)

The first step is the preparation of platelet suspensions. Blood of group O (Rh positive) is collected from a donor who has never previously received blood or plasma transfusions. By means of a previously described two-syringe technic[9] 9 cc. of blood is collected in 1 cc. of 1 per cent Sequestrene-Na₂ solution (1 gm. of Sequestrene Na₂ and 0.7 gm. of NaCl in 100 cc. of distilled water) and centrifuged at 1000 rpm for fifteen minutes in refrigerated centrifuge at 4°C. The upper two thirds of the supernatant plasma are separated and, if the plasma contains more than 2 red or white blood cells per low-power field, respun at 1000 rpm for ten minutes at 4° C. Platelets are counted by a modification of the method previously described,[10] using 1 per cent Sequestrene-Na₂ as anticoagulant and diluting fluid and the count adjusted to 200,000 per cubic millimeter by dilution of the plasma, when necessary, with platelet-poor plasma of the same donor. The platelet-rich plasma is obtained from blood collected in the same manner, but centrifuged at 4000 rpm for an hour at 4° C. Platelet suspensions in plasma are kept in the refrigerator at 4°C. until used and, in any case, not longer than four hours.

The second step consists in the preparation of platelet-poor plasma from the patient. Blood is collected with the same technic outlined in the first step and centrifuged at 4000 rpm for an hour at 4°C. The upper two thirds of the supernatant plasma are separated and, until used, kept in the refrigerator at 4°C. in stoppered containers. These plasmas can also be frozen and kept at −20°C. until used. They should not, however, be refrozen after being brought back to room temperature.

The third step is the detection of platelet agglutinins; 0.1 cc. of platelet suspension in plasma and 0.1 cc. of the patient's platelet-poor plasma are transferred to serology test tubes, 8 by 75 mm., which are stoppered tightly and kept at room temperature for sixty minutes. At the end of the period of incubation, the test tubes are centrifuged at 500 rpm for two minutes and shaken gently to resuspend the platelets. One drop is then transferred to a slide coated with a solution of ten per cent Silicone (Dri Film 9987) in petroleum ether (they are immersed in the solution for thirty minutes, rinsed repeatedly with tap and distilled water and kept under distilled water until used, when they are dried with clean, lint-free gauze), covered with a chemically clean cover slide and observed under high, dry magnification for the presence of platelet clumps.

likelihood, are their disintegration products. These are found abundantly in bank blood, even though few intact platelets are present. Another possibility for the development of resistance to repeated platelet transfusions is that of blood-group or intragroup incompatibility. Our present studies indicate that several platelet groups and types exist.[16] Thus, the development of resistance to platelet transfusions and of antiplatelet agglutinins may be due to the development of platelet agglutinins following the administration of mismatched thrombocytes. When resistance has developed, the patient responds equally poorly to the administration of platelets from every normal available donor. These various findings are of importance since they indicate a real limitation to the effectiveness of platelet transfusions in chronic thrombocytopenic states. They also seem to afford further proof of the immunologic nature of the pathogenic mechanism of idiopathic thrombocytopenic purpura.

Summary and Conclusions

Methods for the transfusion of large numbers of platelets and for their separation and concentration have been developed in recent years. As judged by rate of survival of injected platelets, by their ability to correct the hemostatic defect of thrombocytopenic patients in vivo and the coagulation abnormality of native platelet-poor plasma in vitro, the various methods are not equally effective. The best form of administration of platelets seems to be the direct transfusion of polycythemic blood with the use of multiple Silicone-coated syringes; slightly less effective is the administration of blood collected in completely plastic or Silicone-coated sets, by means of acid citrate dextrose solution or the calcium-complexing agent Sequestrene-Na$_2$ as anticoagulant.

Platelets separated and resuspended in their own plasma or isolated by various procedures and resuspended in saline or other isotonic solution show markedly reduced survival time in vivo, but their favorable influence on the hemostatic mechanism and the bleeding manifestations of thrombocytopenic patients is still noticeable. The introduction of agents giving glass and metal the properties of nonwettable surfaces and of surface-active agents preventing irreversible agglutination of platelets has greatly favored the development of methods for the collection, separation and administration of platelets. The development of mediums in which platelets can maintain their full physiologic attributes for longer periods is to be anticipated in the near future.

The survival rate of platelets administered directly as platelet-rich polycythemic blood into patients with secondary thrombocytopenic purpura is four or five days. It is, however, drastically reduced when a transfusion reaction occurs; when acute, uncontrollable bleeding is present; in patients with marked splenomegaly; in cases of idiopathic thrombocytopenic purpura (especially of the acute variety); and as a result of the development of platelet agglutinins in patients who have received multiple platelet transfusions. The last finding indicates a potentially significant limitation to the use of platelet transfusions in the treatment of thrombocytopenic states.

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THE USE OF LEVO-DROMORAN TARTRATE (LEVORPHAN TARTRATE) FOR RELIEF OF POSTOPERATIVE PAIN*

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IT HAS long been recognized that the spatial configuration of optically active compounds can exert an important influence on their pharmacologic action.[1] Either the levorotatory or the dextrorotatory form of such compounds may have a greater pharmacodynamic effect on certain tissues than its optical antipode. Usually, the levorotatory isomers are more powerful, but sometimes — for example, with amphetamine[2] or acetylmethadol[3] — the dextroisomer has greater activity. Occasionally the activity of one of the isomers is negligible.[4] In other cases competitive antagonism exists between the two isomers. This has been shown for Neo-Synephrine and Sympatol.[5]

Recently, a new synthetic, morphine-like compound *d*, *l*-Dromoran Hydrobromide (*d*, *l*-3-hydroxy-N-methylmorphinan hydrobromide) was evaluated as an analgesic agent for preoperative preparation,[6] in postoperative pain[6-8] and in intractable pain.[9, 10] It has been known for some time, from both animal experiments[11-13] and observations in patients addicted to drugs,[14] that the dextrorotatory isomer of 3-hydroxy-N-methylmorphinan has no morphine-like effects and that the analgesic potency of the racemic form of Dromoran resides wholly in the *l*-isomer. In view of these findings, it was of interest to determine whether Levo-Dromoran could be safely and effectively substituted for the dextrolevorotatory form of the drug in clinical medicine. Although this seemed likely, it was possible that the dextroisomer, present in the racemate, might, in man, alter the duration of action or the safety of the levorotatory form by influencing its rate of excretion or its detoxification, or both. Therefore, an investigation was undertaken to determine the merits of Levorphan§ for the relief of pain after operation.

TABLE 1. *Age Distribution of Patients.*

AGE	PATIENTS RECEIVING *l*-DROMORAN TARTRATE	PATIENTS RECEIVING *d,l*-DROMORAN HYDROBROMIDE	PATIENTS RECEIVING MORPHINE SULFATE
yr.			
11–20	9 (2.9%)	8 (2.6%)	7 (2.2%)
21–30	30 (9.6%)	31 (10.0%)	36 (11.6%)
31–40	81 (26.0%)	62 (20.0%)	58 (18.6%)
41–50	79 (25.4%)	100 (32.2%)	111 (35.6%)
51–60	67 (21.5%)	73 (23.4%)	62 (19.9%)
61–70	35 (11.3%)	34 (10.9%)	34 (10.8%)
71–80	10 (3.2%)	3 (0.9%)	4 (1.3%)
Totals	311	311	312

TABLE 2. *Types of Operations.*

OPERATION	PATIENTS RECEIVING *l*-DROMORAN TARTRATE	PATIENTS RECEIVING *d,l*-DROMORAN HYDROBROMIDE	PATIENTS RECEIVING MORPHINE SULFATE
Thyroidectomy	19 (6.1%)	3 (0.9%)	3 (0.9%)
Thoracotomy and thoracoplasty	12 (3.8%)	17 (5.5%)	17 (5.5%)
Gastric resection	26 (8.4%)	12 (3.9%)	13 (4.2%)
Cholecystectomy	44 (14.1%)	62 (19.9%)	62 (19.7%)
Incisional and ventral herniorrhaphy	14 (4.5%)	14 (4.5%)	14 (4.5%)
Abdominoperineal resection and colectomy	6 (1.9%)	11 (3.5%)	11 (3.5%)
Appendectomy	23 (7.4%)	13 (4.2%)	13 (4.2%)
Inguinal herniorrhaphy	43 (13.8%)	35 (11.2%)	37 (11.8%)
Hysterectomy	33 (10.6%)	51 (16.4%)	49 (15.7%)
Vaginal plastic procedure and hysterectomy	8 (2.6%)	6 (1.9%)	6 (1.9%)
Vaginal plastic procedure alone	14 (4.5%)	12 (3.9%)	11 (3.5%)
Nephrectomy	3 (1.0%)	4 (1.3%)	4 (1.3%)
Nephropyeloureterolithotomy	1 (0.3%)	10 (3.2%)	10 (3.2%)
Suprapubic prostatectomy		7 (2.2%)	7 (2.2%)
Hemorrhoidectomy	6 (1.9%)	6 (1.9%)	5 (1.6%)
Laminectomy	22 (7.1%)	12 (3.9%)	12 (3.9%)
Hip nailing and hip reconstruction	9 (2.9%)	4 (1.3%)	4 (1.3%)
Arthrotomy of knee	8 (2.6%)	4 (1.3%)	5 (1.6%)
Miscellaneous procedures*	20 (6.4%)	28 (9.0%)	29 (9.3%)
Totals	311	311	312

*The "miscellaneous" group included prefrontal lobotomy, excision of neck tumor, open reduction of clavicle, open reduction of humerus, open reduction of elbow, repair of arm laceration, radical mastectomy, mastectomy, repair of diaphragmatic hernia, sympathectomy, lysis of abdominal adhesions, spinal fusion, cesarean section, colostomy, celectomy, excision of pilonidal cyst, coccygectomy, resection of bladder diverticulum, orchidectomy, hydrocelectomy, multiple venous ligations, amputation of leg, open reduction of tibia, open reduction of ankle and amputation of toe.

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§The levorotatory Dromoran, in the form of Levorphan tartrate, was kindly supplied by Hoffmann-LaRoche, Incorporated, Nutley, New Jersey.

Methods and Material

The selection of patients and the method of evaluation were similar to the procedures used in a previous study, in which the effects of *d,l*-Dromoran Hydrobromide and morphine sulfate in postoperative pain were compared.[7] By means of the same experimental approach the results with Levorphan tartrate in the present investigation could be correlated with the findings of the previous study. Instead of the 5-mg. doses of the racemic form of Dromoran Hydrobromide, the theoretical equivalent — that is, 3-mg. doses of Levorphan tartrate — was administered. The present series comprises 311 patients who received a total of 1067 subcutaneous injections of the levorotatory form of the drug. Table 1 shows the age distribution of these patients, and Table 2 summarizes the incidence of the various operations performed on them. In both tables these data are correlated with the corresponding data pertaining to the groups of patients previously studied, who received *d,l*-Dromoran Hydrobromide and morphine sulfate, respectively. As in the former series, the resulting relief of pain was recorded as complete when the patient had no pain for three hours or more, moderate when complete or almost complete relief was obtained for less than three hours, slight with partial relief for less than three hours and none. The following side effects were looked for: dizziness, nausea, vomiting, diaphoresis, dryness of mouth, anorexia, pruritus, weakness, headache, drowsiness, confusion, visual disturbances, tachycardia and chills.

Results

Relief of Pain

The summary of the findings with Levorphan tartrate are presented in Table 3, which also compares these results with those previously recorded for the racemic form of the drug and for morphine sulfate. It can be seen that the first postoperative dose of Levorphan tartrate afforded complete relief in 77.2 per cent of the cases. The incidence of complete analgesia after the first dose of *d,l*-Dromoran Hydrobromide and morphine was 66.5 per cent and 46.2 per cent respectively. The first dose of Levorphan tartrate had no analgesic effect in 1 per cent of the patients. The corresponding figure was 2.6 per cent for *d,l*-Dromoran Hydrobromide and 5.8 per cent for morphine. Similarly, all doses of both the levoisomer of Dromoran and the racemic form of the drug gave complete relief in a higher percentage of cases (77.5 per cent and 75 per cent respectively) than corresponding doses of morphine (54.7 per cent).

Side Effects

The incidence of diaphoresis was lower with Levorphan tartrate than with morphine, whereas the opposite was true of *d,l*-Dromoran Hydrobro-

Table 3. *Comparative Effects of l-Dromoran Tartrate, d,l-Dromoran Hydrobromide and Morphine Sulfate*

Drug	No. of Cases	Total No. of Doses	Average Age	Average Total No. of Doses per Patient	Relief Obtained with 1st Dose: Complete		Moderate		Slight		None		Average Duration of Relief after 1st Dose	Relief Resulting from All Doses: Complete		Moderate		Slight		None		Side Effects of 1st Dose: Diaphoresis		Dryness of Mouth		Anorexia		Pruritus		Weakness		Headache		Drowsiness		Glogginess		Mental Confusion		Visual Disturbance		Tachycardia		Chills		Nausea		Vomiting		Total Side Effects from All Doses
			First 24 hr.		no.	%	no.	%	no.	%	no.	%	hr.	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
l-Dromoran Tartrate	311	1067	1.8	3.4	240	77.2	60	19.3	8	2.6	3	1.0	5.5	827	77.5	184	17.2	36	3.4	20	1.9	2	0.6	28	9.0	16	5.1																				
d,l-Dromoran Hydrobromide	311	1336	2.1	4.0	207	66.5	65	20.9	31	10.0	8	2.6	6.1	1004	75.0	231	17.4	80	6.0	21	1.6	5	1.6	26	8.4	11	3.5																				
Morphine sulfate	312	1097	2.3	3.4	144	46.2	100	32.0	5	16.0	18	5.8	5.8	601	54.7	333	30.3	128	11.7	35	3.3	5	1.6	38	12.2	25	8.0																				

Table 3 (*Concluded*).

Drug	Side Effects of 1st Dose: Diaphoresis		Dryness of Mouth		Anorexia		Pruritus		Weakness		Headache		Drowsiness		Glogginess		Mental Confusion		Visual Disturbance		Tachycardia		Chills		Nausea		Vomiting		Total Side Effects from All Doses
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
l-Dromoran Tartrate	34	10.9	15	4.8	0	—	3	1.0	0	—	4	1.3	25	8.0	6	1.9	1	0.3	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	240	22.5
d,l-Dromoran Hydrobromide	66	21.2	15	4.8	1	0.3	3	1.0	8	2.6	2	0.6	24	7.7	7	2.2	3	1.0	2	0.6	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—	317	23.7
Morphine sulfate	53	17.0	5	1.8	0	—	6	2.0	0	—	5	1.8	17	5.5	1	0.3	2	0.6	1	0.3	2	0.6	1	0.3	236	21.5																				

mide. The frequency of all other side reactions recorded was approximately the same for levorotatory Dromoran and its racemic form.

Discussion

The difference in the incidence of complete relief of pain afforded by all doses of Levorphan tartrate on the one hand and of *d,l*-Dromoran Hydrobromide on the other (Table 3) is not significant. However, statistical evaluation of the data pertaining to the first doses of these two drugs indicates that the incidence of complete analgesia from 3 mg. of Levorphan tartrate is significantly higher than that from 5 mg. of *d,l*-Dromoran Hydrobromide. The observation that a dose of the levo-Dromoran compound has greater analgesic activity than the quantity of the racemic drug that contains the amount of the levoisomer used alone might be explained by the findings of Slomka and Gross,[15] who showed that the dextro-isomer has an inhibitory effect on Levorphan analgesia. It appears also from Table 3 that doses of either 3 mg. of Levorphan tartrate or 5 mg. of *d,l*-Dromoran Hydrobromide gave complete relief in a higher percentage of cases than doses of 10 mg. of morphine sulfate. The fact that the analgesic effect of 3 mg. of Levorphan tartrate is at least equal to that of 5 mg. of *d,l*-Dromoran Hydrobromide constitutes indirect evidence that the dextroisomer is devoid of pain-relieving qualities and substantiates the pharmacologic finding that the analgesic potency of the racemic compound resides in the levoisomer. The substitution of the levorotatory form of Dromoran for its racemate was not attended by a higher incidence of side effects. It is doubtful whether the less frequent occurrence of diaphoresis observed with the levoisomer as compared with the racemate is a significant finding. It can be concluded that, for relief of postoperative pain, the effects of 3 mg. of Levorphan tartrate are at least equal to those of 5 mg. of *d,l*-Dromoran Hydrobromide and that the two drugs can be used interchangeably in these doses. Further clinical observations will have to be made to decide whether 2 mg. of the levoisomer would furnish the same analgesic potency as 5 mg. of the racemic compound.

The resolution of *d,l*-Dromoran into its optically active components provided a compound — levo-Dromoran — that has at least twice the analgesic potency of the racemic mixture. From the pharmacologic and pharmaceutical points of view, this separation may well be regarded as a distinct advance.

Summary and Conclusions

One thousand and sixty-seven doses of *l*-Dromoran (Levorphan) [Tartrate (3 mg.) were administered subcutaneously to 311 patients for relief of postoperative pain. The first postoperative dose gave complete relief in 77.2 per cent of the cases, the average duration of analgesia lasting five and a half hours. Complete relief of pain after all doses was obtained in 77.5 per cent.

These figures were compared with those recorded for a similar group of surgical patients who received the theoretical equivalent of *d,l*-Dromoran Hydrobromide (5 mg.). A higher percentage of patients derived complete analgesia from the first dose of Levorphan tartrate than from the first dose of *d,l*-Dromoran Hydrobromide, but results of subsequent doses were approximately equal.

The incidence of side effects was not greater with Levorphan tartrate than with the racemic drug.

From the clinical point of view 3 mg. of Levorphan tartrate and 5 mg. of *d,l*-Dromoran Hydrobromide are interchangeable.

Regarding analgesic potency and incidence of side effects, 3 mg. of Levorphan tartrate compared favorably with 10 mg. of morphine sulfate.

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THERAPEUTIC EFFECT OF ACTH IN STEVENS-JOHNSON SYNDROME (ERYTHEMA MULTIFORME EXUDATIVUM)

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THE purpose of this paper is to report on the therapeutic effect of ACTH in a case of Stevens-Johnson syndrome (erythema multiforme exudativum). A few cases similarly treated have been reported. Bleier and Schwartz[1] started a twenty-four-year-old male patient on cortisone because of persistent eye symptoms and continuous

FIGURE 1. *Appearance of the Patient on November 16, after He Had Received Approximately 12,000,000 units of Penicillin and Some Chloramphenicol during the Previous Four Days.*

The ulcerations on the tongue and lips had become progressively worse. Pain had made eating almost impossible.

appearance of new lesions on the skin. An excellent response was noted within twenty-four hours.

Wammock, Biederman and Jordan[2] reported the use of ACTH in a twenty-three-year-old soldier and noted excellent response within 24 hours.

Agostas et al.[3] reported 2 cases. The first patient, a twenty-two-year-old woman, showed excellent response to ACTH within forty-eight hours. The second patient was a fourteen-year-old boy. On March 24, 1951, cortisone therapy was started, and a good response occurred within twenty-four hours. He had a recurrence and was readmitted to the hospital on May 11. This time ACTH was used and failed to produce a response after four days. When the treatment was changed to cortisone the therapeutic response was excellent within forty-eight hours.

CASE REPORT

R. V., a 16-year-old boy, was admitted to St. Mary's Hospital on November 12, 1951, complaining of severe sore throat, photophobia and bleeding of the gums.

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The illness had begun on November 4, and he was first seen by his family doctor the next day, when he complained of a slight cold and a sore mouth. On examination the mouth and pharynx were not abnormal except for a cluster of blebs, between the upper lip and the gum, that looked like small grapes. The temperature was 101°F. He was given 500,000 units of penicillin and told to use an alkaline mouth wash. He was seen again on November 7, when the mouth had become much sorer and was lined with a whitish exudate. The lips were swollen and red; the temperature was 101°F. To investigate the possibility that this was a severe Vincent infection, cultures of the throat and mouth were taken, but Vincent's organisms were not found. The patient was given 2 cc. of a bismuth preparation and 1,000,000 units of penicillin intramuscularly. On the following day severe conjunctivitis and photophobia were present. The temperature was 102°F., and the patient was referred for eye, ear, nose and throat consultation. He was continued on penicillin, and throat cultures were repeated, again being negative for Vincent's organisms. Because he was not responding to treatment, was unable to eat and was in severe distress owing to soreness of the mouth and eyes, he was sent to the hospital.

FIGURE 2. *Appearance of the Patient on November 20, after Four Days of ACTH.*

All ulcers on the lips have healed, and there is no longer any bleeding. The lesions of the tongue are reduced but still present, though not painful.

Examination showed an acutely ill boy. There were 6 to 8 discrete, erythematous, 1-cm. lesions on the legs, some with central bullae. The lesions were asymptomatic, and the patient had not even noticed them. Photophobia was severe. The conjunctivas were injected and swollen, with a purulent discharge. The ears were normal. There were ulcers on both sides of the nasal septum, with a whitish membrane. The lips were ulcerated; the buccal mucosa was also ulcerated, with many bleeding points and a patchy, white membrane. The heart and lungs were normal. Examination of the abdomen, extremities and nervous system was negative.

The temperature was 103°F., the pulse 102, and the respirations 24. The blood pressure was 144/88.

Examination of the blood revealed a red-cell count of 5,220,000, with a hemoglobin of 15.9 gm. per 100 cc., and a white-cell count of 13,650, with 34 per cent segmented and 20 per cent nonsegmented neutrophils, 3 per cent eosinophils, 2 per cent monocytes and 41 per cent lymphocytes. Three

were 20 per cent abnormal lymph forms. The platelets numbered 235,000 per cubic millimeter. The urine gave negative tests for sugar and albumin, and the sediment contained many white cells. The blood Kahn reaction was negative, as was a bone-marrow examination. Heterophil-antibody agglutination tests were positive in a titer of 1:14. An x-ray film of the chest showed an area of increased density in the left lower lobe.

During the first 4 hospital days the patient received large doses of penicillin, chloramphenicol, Benadryl and ophthalmic ointments. The temperature remained elevated up to 104°F. The throat and buccal mucosa showed more severe ulcerations (Fig. 1). The conjunctivitis and photophobia also increased. The eyelids became markedly edematous. A purulent urethritis was noticed on the 2d day. The skin lesions increased rapidly. The few lesions first noticed on

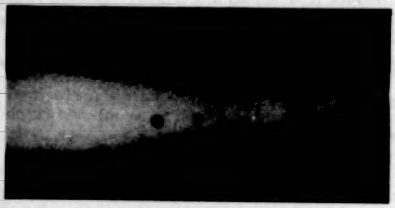

FIGURE 3. *Discrete Erythematous Lesions, with a Central Area of Discoloration and Bullous Formation, Which Appeared on about the Fourth Day of Illness. Under ACTH therapy they rapidly decreased.*

the right leg spread over both thighs and the scrotum. By the 5th hospital day, his condition had become critical.

At this time all previous medication was discontinued, except for an ophthalmic ointment of 2 per cent yellow oxide of mercury, and the patient was given 25 mg. of ACTH every 6 hours. The response was dramatic. Within 12 hours he was able to swallow and chew food. No new skin lesions appeared, and the old ones regressed to small dry scaly areas (Fig. 2). The temperature dropped to normal within 6 hours and remained normal. The urethritis disappeared within 48 hours. The stomatitis improved more slowly, and all lesions were not considered healed till the 9th hospital day, or 4 days after ACTH had been started (Fig. 3).

The patient was continued on ACTH for a total of 10 days. There were no flare-ups of any of the symptoms, and he was discharged on the 20th day.

He was last seen on December 27. All the lesions had healed, and he was feeling well.

DISCUSSION

One of the most confusing chapters in present-day medical literature deals with erythema multiforme exudativum. The syndrome includes conjunctivitis, stomatitis and urethritis associated with skin lesions. The cutaneous lesions vary from macules and papules to vesicles and bullae on an erythematous base. The bullae may rupture, leaving an adherent hemorrhagic crust. The lesions are nonpainful and nonpruritic, being most numerous on the extremities. Since 1916, succeeding investigators have described at least four syndromes that are similar in most respects.

In 1916 Reiter[4] reported a disease occurring in German soldiers that consisted of urethritis, conjunctivitis and arthritis. Subsequent reports by Epstein[5] and others mentioned cutaneous manifestations. The etiology of Reiter's disease was never certified, although the gonococcus and the spirochete were suspected.

In 1922 Stevens and Johnson[6] described 2 cases of an eruptive fever associated with stomatitis and ophthalmia. Later observers mentioned other symptoms such as tracheobronchial and pulmonary involvement, severe toxemia and malaise, nausea, vomiting and hematemesis. The etiology of the Stevens–Johnson syndrome, as it became known, was not clear. *Staphylococcus aureus* and Vincent's organisms had been isolated from ulcerated lesions, but it seemed likely that they were secondary invaders. Virus studies were done, but their results were not confirmed.

In 1937 Klauder[7] called attention to a syndrome described by Rendu[8] in 1916. It involved the mucous membranes of the mouth, conjunctiva and urethra and was associated with vesicular eruptions on the extremities. Fiessinger et al.[9] designated it as ectodermosis erosiva pluriorificialis in 1923. The etiologic organism was not isolated, although a virus was suspected, and a similarity to the well known hoof and mouth disease occurring in animals was emphasized.

In 1937 Behcet[10] described a disease characterized by a triple complex of ulcers in the mouth, ulcers on the genitalia and episcleritis and erosions on the cornea. Symptoms such as joint involvement were added by other observers. The etiology was again suspected of being a virus. Inclusion bodies were found in only 1 case but later on could not be verified.

It is obvious that the similarities between these four syndromes described by the different authors are more apparent than the differences. The question whether they are all describing the same condition has tempted others. Robinson and McCrumb,[11] in an excellent review on mucocutaneous ocular syndromes, suggest that they are probably all variants of erythema multiforme exudativum.

The diagnosis of this condition may, during the early stages, be easily confused with Vincent's angina, infectious mononucleosis, leukemia, gonorrhea, arthritis, conjunctivitis and other infectious diseases. When the patient fails to respond to antibiotics and more symptoms progressively develop, the true syndrome usually becomes clear.

From the description of previous reports the disease seems to be self limited in most cases, although deaths have been reported. How many milder cases of this disease have been misdiagnosed is an interesting question. The possible connection with animal diseases is important and should be kept in mind. In the case presented above, the patient had ample contact with the usual farm ani-

mals. As far as could be determined, none of these had any unusual sicknesses.

Summary

Another case of a favorable response in the treatment of erythema multiforme with ACTH is reported. The confusing picture of the disease in its developing stages is emphasized.

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ADRENOCORTICAL FUNCTION IN ANOREXIA NERVOSA BEFORE AND AFTER LOBOTOMY*

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CLINICAL differences between anorexia nervosa and panhypopituitarism are usually so striking that differentiation of these two disorders is not difficult.[1] There are also important physiologic differences. Nevertheless, the idea persists in some quarters that the physical manifestations of anorexia nervosa are partly due to secondary hypoadrenalism and that ACTH (adrenocorticotrophic hormone) should have a specific, beneficial effect. Observations on adrenocortical function in anorexia nervosa made at this hospital and elsewhere may be of interest in this connection.

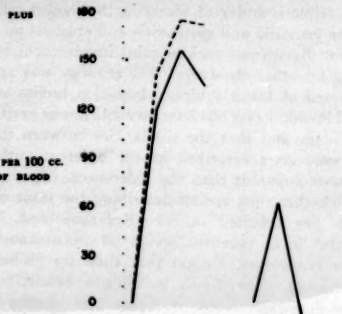

FIGURE 1. *Glucose Tolerance Curves before and Several Months after Lobotomy.*

The broken line shows the effect of 25 mg. of ACTH on glucose tolerance.

Material and Methods

A nineteen-year-old girl with anorexia nervosa was studied at McLean Hospital; the clinical manifestations of her disorder have already been reported.[2] Observations were made when the patient weighed 75 pounds and again, two months after partial lobotomy, when she weighed 110 pounds owing to increased food intake, almost wholly carbohydrate.

The method of Forsham et al.[3] was used to count blood eosinophilic cells. The blood sugar was measured by the method of Folin and Wu[4]; urinary 17-ketosteroid output was estimated by the method of Callow, Callow and Emmons,[5] and the urinary estrogen output by that of Engel and his associates.[6]

Observations

Blood Eosinophilic Cells

Three blood eosinophil counts made prior to operation were between 44 and 50 per cubic millimeter; the average was 47. The intramuscular injection of 25 mg. of ACTH caused a decrease of 75 per cent in the blood eosinophil count at four hours. Intramuscular injection of 0.01 mg. of epinephrine per kilogram of body weight resulted in a fall of 55 per cent in the count at four hours.

Four eosinophil counts made two months after lobotomy ranged between 41 and 125, averaging 81 per cubic millimeter — a value not significantly different from the preoperative level.

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17-Ketosteroid Excretion

Measurements of 17-ketosteroid output on four days some weeks before operation yielded values of 2.5 to 2.7, averaging 2.6 mg. per twenty-four hours.

Two months after lobotomy, two measurements revealed values of 12.2 and 14.7, averaging 13.5 mg. per twenty-four hours.

Glucose Metabolism

The fasting blood sugar level was between 81 and 98 mg. per 100 cc. before operation; it was 95 mg. two months after lobotomy. Blood sugar levels after ingestion of 100 gm. of glucose were abnormally high in a study made before operation. Ingestion of 100 gm. of glucose after intramuscular injection of 25 mg. of ACTH revealed an even more abnormal curve (Fig. 1). Two months after operation, at a time when the patient had been gorging herself on sweets for some weeks, the glucose-tolerance curve was found to be normal (Fig. 1).

Estrogen Output

The urinary estrogen excretion was 99 gamma per twenty-four hours two months after lobotomy.

Discussion

The common finding of decreased urinary excretion of 17-ketosteroids in patients with anorexia nervosa[7-14] has led many workers to conclude that decreased adrenocortical function is present in that disease. However, the 17-ketosteroid output may be in the normal range in anorexia nervosa.[10, 11, 14, 15] Slightly low values were found in the patient under discussion, but they were not as low as those found in panhypopituitarism. It is known that starvation often causes a marked diminution in excretion of these steroids[9, 16]; in clinical practice similar decreases in patients with emaciation caused by a variety of diseases are common. Although the literature contains a report of decreased corticoid excretion in a patient with anorexia nervosa,[12] no such finding was observed by Venning and Browne[14] or by Talbot et al.[17] The occurrence of decreased excretion of 17-ketosteroids and normal or even increased outputs of corticoids suggests that the transformation of corticoids into 17-ketosteroids is impaired in anorexia nervosa. Hepatic disease may cause this phenomenon[18]; the development of hepatic dysfunction in starvation is well known. It is probable that the decreased 17-ketosteroid excretion that is often found in anorexia nervosa has been misinterpreted. Long[19] has commented on the inutility of measurement of 17-ketosteroid output as an index of adrenocortical function. After operation, the patient described here increased her caloric intake greatly, and the urinary 17-ketosteroids rose to a level high for her age. These findings corroborate Hemphill's[20] earlier observations on the effects of lobotomy in an emaciated male patient; Reiss[16] and Eitinger[7] also found that increased caloric intake raised the 17-ketosteroid output markedly in anorexia nervosa.

The report by Greenblatt et al.[21] of a normal Kepler test in anorexia nervosa also rules out the possible occurrence of adrenal insufficiency secondary to pituitary disease in this condition. The normal eosinopenic response to ACTH reported by Greenblatt, Barfield and Clark[21] and Shadaksharappa and his co-workers[12] was corroborated in the present study. The eosinopenic response to epinephrine was also in the normal range in the patient described above; Shadaksharappa et al.[12] found it to be slightly diminished in their patient.

The abnormal glucose-tolerance test was apparently a result of starvation, since the curve was normal after operation when the patient took a high-carbohydrate diet. At any rate, the results of the test do not support a diagnosis of adrenal insufficiency. Further impairment of glucose tolerance after injection of as little as 25 mg. of ACTH is often found in patients with severe neurosis.[22]

It is evident, therefore, that anterior-pituitary-adrenocortical function is not depressed in anorexia nervosa; if anything, the tendency toward lowered eosinophilic cell counts and the development of hirsutism suggests that the adrenal cortex is hyperactive. The clinical improvement that followed lobotomy in the case described above was not caused by — or even associated with — improved adrenocortical function. There is good evidence of impairment of other endocrine organs in anorexia nervosa; the physiologic picture is therefore identical with that found in experimental starvation in animals — that is, atrophy of all endocrine glands except the adrenal. Certainly, there is nothing to indicate that ACTH or any other known hormone has a specific effect in anorexia nervosa. The fact that only a minority of patients with the disorder improve when given cortisone or ACTH suggests that the apparent effect of these substances is not a specific one.

Summary and Conclusions

Studies of adrenocortical function were made in a patient with anorexia nervosa before and again several months after lobotomy.

Available evidence shows that adrenocortical function and reactivity are not depressed in anorexia nervosa.

Lobotomy in the patient discussed caused clinical improvement; no increase in adrenocortical activity occurred with improvement.

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MEDICAL PROGRESS

SPATIAL VECTORCARDIOGRAPHY*

Review and Critique

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ELECTROCARDIOGRAPHY has yielded considerable knowledge concerning the electric phenomena associated with activity of the heart. This method of examination has been thoroughly explored, and it is unlikely that its usefulness will be extended to any important degree. The investigation of other methods of studying the cardiac potential differences, therefore, has been welcomed by those interested in increasing knowledge in this field. The most fruitful of these methods is that which has come to be known as spatial vectorcardiography.

A force having magnitude, direction and sense can be represented as a vector. At each instant during cardiac activity all electrical forces summate into one manifest force having these properties. This manifest force, or resultant vector, is called the "cardiac vector." Electrocardiographic leads are scalar§ derivatives that record the projection of the instantaneous cardiac vectors on the lead axes. On the other hand, the vectorcardiogram is a curve on which all points represent the termini of successive resultant vectors, changing in direction and magnitude from instant to instant, as the potential differences resulting from activation and resovery of the myocardium wax and wane with each heart beat.

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§A scalar quantity has magnitude and sense (positive or negative) but not direction. Examples are temperature, mass and time.

This review of vectorcardiography concerns its history, principles, technics, relation to electrocardiography, clinical application and place in medicine.

HISTORICAL DEVELOPMENT

Interest in bioelectric phenomena goes back to 1786, when Galvani postulated that muscle contraction in the frog was associated with the flow of an electric current. Such phenomena were actually observed in connection with activity of the heart, and a great impetus for their study was provided by the application of the capillary electrometer for this purpose by Waller.[1] This set the stage for the development of electrocardiography and vectorcardiography, awaiting only the introduction of suitable instruments.

The observations of Waller, reported in 1889, indicated that he had a clear understanding that the extremity potentials were related to the spatial position of the electric forces generated during the heart beat. Thus, the study of spatial forces, far from being a new development, had its birth in the concepts of the first observer to record the electric currents produced by the human heart.

These concepts were extensively elaborated by Einthoven, Fahr and de Waart[2] in 1913, when they demonstrated the influence of the respiratory variations of heart position on the extremity potentials. They were able to do this by devising a method of finding the manifest magnitude and direction of any instantaneous resultant cardiac electromotive

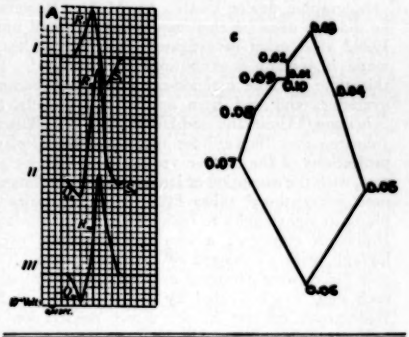
force, based on the equilateral triangle, by making use of the bipolar limb leads. They computed the manifest resultant cardiac electromotive force at ten successive instants during the QRS interval, and thus, in effect, were the first to depict the spatial cardiac vectors as projected onto the plane (frontal) defined by the limb leads (Fig. 1).

The following year Williams[3] used this method to investigate the cause of the phase difference frequently observed between homonymous peaks of the electrocardiogram by constructing the "vector diagram." The last was a series of vectors that he obtained by plotting synchronous potential differences at different instants of the QRS interval of simultaneously recorded Leads 1 and 2, or Leads 1 and 3. He emphasized the fact that the potential fluctuations accompanying cardiac contraction are vector quantities, and that the electrocardiogram is a function of the path pursued by the wave of activity that spreads through the heart during a contraction. Lewis[4] made use of a similar method in his studies of left ventricular hypertrophy, bundle-branch block and auricular flutter; and Fahr,[5] in 1920, extended still further the concept of vector interpretation of the electrocardiogram.

An important contribution to vectorcardiography was made by Mann[6] in 1920. He was impressed by Williams' paper,[3] which he read in 1916, and four years later he gave an account of his investigations. Instead of using the manifest vector E and angle α to define the position of a point (polar co-ordinates), he found two values corresponding to X and Y in the rectangular system of co-ordinates, X being equal to e^1, and Y to $\frac{e^2 + e^3}{\sqrt{3}}$.* He plotted successive values of X and Y, using the center of Einthoven's triangle as the common origin, through a complete cardiac cycle, and connected the consecutive points with a fairly smooth curve. This curve he called the "monocardiogram," to distinguish it from the ordinary electrocardiogram, which he referred to as a "tricardiogram" or threefold derivative of the monocardiogram. He appreciated the fact that the shape of the electrocardiogram was due to the projections of the monocardiogram on the sides of an equilateral triangle, and he had the imagination and foresight to suggest that three leads taken in a horizontal plane would furnish a "transverse monocardiogram" and thus a three-dimensional view of events during the cardiac cycle.

As important as these contributions were, the method was based on analysis of the electrocardiogram and, in this sense, was of limited value. Nevertheless, these studies emphasized some important concepts. Each point on the monocardiogram represents the terminus of an instantaneous resultant, and a complete picture is thus obtained of the constantly changing direction and magnitude of the cardiac vectors as the excitatory process reaches its full development and then declines. Since this curve is a vector function of time, Wilson and Johnston[7] later introduced the term vectorcardiogram to emphasize the true nature of the difference between it and the electrocardiogram, which is a scalar function of time.

The widespread adoption of Mann's method was also hindered by the difficulty of constructing the monocardiogram. The next important advance in the study of the cardiac vector had to await the development of instruments that would yield the curves directly, just as in an earlier era the full development of electrocardiography had to await Einthoven's string galvanometer. Again, Mann[8, 9] provided a far-reaching stimulus with his early experiments in devising an instrument that would record the monocardiogram directly. In 1924 he produced an instrument that consisted essentially of two three-stage amplifiers actuating a cathode-



B

Zeit in Sek.	Potentialunterschiede in Zehntel eines Millivolts bei den Ableitungen I	II	III	Resultierender Potentialunterschied Richtung	Manif. Größe 10^{-4} Volt
0,01	0	0	0	—	0
0,02	0	−1,5	−1,5	−90°	1,7
0,03	2,0	−2,5	−4,5	−64°	4,5
0,04	4,5	3,5	−1,0	18°	4,7
0,05	7,5	13,0	5,5	55°	13,0
0,06	2,0	18,0	16,0	84,5°	19,8
0,07	−4,5	4,5	9,0	120°	9,0
0,08	−3,0	1,0	4,0	136°	4,2
0,09	−1,0	−0,5	0,5	±180°	1,0
0,10	0	0	0	—	0

FIGURE 1. *Spatial Cardiac Vectors Projected onto the Frontal Plane Defined by the Limb Leads.*

A = *three simultaneously recorded limb leads (reproduced from Einthoven et al.*[5]*).*

B = *magnitude and angle α of ten manifest vectors computed from simultaneous limb-lead potentials at 0.01-second intervals (reproduced from Einthoven et al.*[5]*).*

C = *curve constructed by us by connecting the termini of the computed manifest vectors after the manner of Mann.*[6]

*e^1 = Lead 1, e^2 = Lead 2, and e^3 = Lead 3.

ray oscillograph, but had to abandon the method because the oscillographs then available were unsatisfactory.[9] In1931 he demonstrated a galvanometer that was capable of responding simultaneously to three "separate and independent" (*sic*) electric currents. It was actuated by three amplifiers, one corresponding to each limb lead of the electrocardiogram, and produced a curve indistinguishable from the mathematically derived monocardiogram. The galvanometer reflected a small, sharp, brilliant spot of light, which was recorded by an ingenious photographic device created by Mann. However, he did not describe this instrument in detail until 1938,[9] after other investigators had independently made important contributions in this field. By this time suitable cathode-ray tubes had become available, and had been applied successfully by Schellong,[10] Hollmann and Hollmann,[11] and Wilson, Johnston and Barker[12] for recording frontal-plane projections of the cardiac vector. These investigators, with the exception of Hollmann and Hollmann, used conventional tubes fitted with two pairs of plates at right angles to each other. Hollmann and Hollmann employed a special cathode-ray oscillograph, with six instead of four pole pieces. The pole pieces were arranged in pairs 120° apart, and each pair was activated by a lead (1, 2 and 3). Widespread interest in the direct registration of vectorcardiograms quickly followed, and attempts were made to record projections other than frontal.[10, 13-21] Schellong[10] recorded sagittal, as well as frontal-plane, projections as early as 1936, and was the first to utilize an orthogonal reference system. Soon thereafter technics were developed that permitted the registration of projections of the spatial loops in any of several planes, as discussed below in the section entitled "Reference Systems."

Methods and Principles

Although the methods of obtaining vectorcardiograms vary widely, the underlying principles are the same and exceedingly simple. The indispensable instruments are a cathode-ray tube, amplifiers, a timing device and a camera. The filament of the tube emits electrons, which are attracted to a positively charged grid with an aperture through which a beam of electrons passes. The distal end of the tube is fitted with a fluorescent screen, and when the beam of electrons impinges on it, a brilliant, luminous spot is produced that is easily visualized and photographed.

The tube most commonly employed is provided with two sets of plates, one vertical and the other horizontal. A potential difference between the vertical plates deflects the beam in the horizontal direction, or X axis, and a potential difference between the horizontal plates deflects the beam in the vertical direction, or Y axis. The amount of displacement is strictly proportional to the magnitude of the difference of potential under the conditions encountered in clinical work. If both sets of plates are utilized simultaneously, the luminous spot occupies a position corresponding to the geometric sum of the horizontal and vertical deflections. Since the cathode-ray tube is an indicating device with a pointer of negligible inertia, movement of the beam is instantaneous, and overshooting does not occur. The cathode-ray tube is not sensitive enough to bring about large deflections of the beam when charged with the small voltages from the heart, and an amplifier for each set of plates is therefore required so that the input voltages can be amplified 50,000 to 250,000 times. Only in this way can sufficient movement of the electron beam be effected to provide satisfactory vectorcardiograms.

The intensity and focusing controls serve to produce a clear image of the luminous spot at the desired intensity. The greater the velocity of electrons constituting the beam, the more intense the image. To protect the fluorescent screen against burning it is possible to control the velocity of the electrons automatically, and thus to reduce the intensity of the image while the slow-moving P and T loops are being inscribed.[22] A standardizing voltage of 1 millivolt is introduced into the input circuit of each amplifier, and the sensitivity controls are turned until the spot moves 2 to 4 inches on each axis on the screen, the choice depending on the size of the natural deflections. On the X axis the spot moves to the observer's right, and on the Y axis it moves down; if both sets of plates are utilized simultaneously, the spot moves down and to the observer's right at an angle of 45°. Greater sensitivity may be obtained if it is desired to study the P or T loops or a portion of the QRS loop, and by means of a positioning system any portion of a deflection that is greater than the full-screen diameter can be centered on the screen.

An electrical tuning fork, or oscillator, is used to interrupt the trace by means of intensity modulation of the cathode-ray beam. This is capable of providing accurate time markings on the trace itself through a wide range. The frequency selected will depend on whether interest centers chiefly in the P, QRS or T loops. For routine work 300 to 500 cycles per second are satisfactory, but 800 to 1000 cycles demonstrate variations in the speed of movement of the luminous spot more clearly; 200 cycles are more suitable for study of the T loop, and 100 cycles for the P loop. It is of considerable importance to know the direction in which a loop is being inscribed. Since it is not always possible to ascertain this by inspection, the tuning fork can be combined with a relaxation oscillator so that a teardrop pattern is produced. In this way, direction of inscription is indicated on the photograph.[23]

A system of electrode placement is selected, as described below under the heading "Reference Systems," and one lead is connected to one set of

plates, and another lead to the other set of plates of the cathode-ray tube. The leads in most reference systems are at right angles to each other and are parallel to the natural co-ordinate axes of the body, X, Y and Z.* The utilization of both sets of plates simultaneously in the manner indicated will yield the resultant between the vertical (Z) and horizontal (X), the horizontal (X) and sagittal (Y), or the vertical (Z) and sagittal (Y) components of the cardiac vector. That is, the instrument finds the vectorial sum of two potential differences, each being the projection of the cardiac vector onto a lead. As the resultant vector changes in direction and magnitude from instant to instant, the luminous spot, which occupies a position corresponding to the termini of successive instantaneous resultants, describes a curve, which is the projection, or vectorcardiogram, of the spatial forces onto a plane. The luminous spot begins and ends at zero, the isoelectric, or O point (point of origin of the vectors), with each cardiac cycle, describing in turn the P, QRS and T loops. If two or more planar projections are obtained, the three-dimensional position of the cardiac vectors can be found, as pointed out below in the section headed "Reference Systems," and are designated PsÊ loop, the QRSsÊ loop and the TsÊ loop. These designations are used to give emphasis to the spatial characteristics of the cardiac vectors, and correspond to depolarization of the atria and depolarization and repolarization of the ventricles, respectively.

Triple scopes with the required number of amplifiers are commercially available so that three projections of the cardiac vector can be registered simultaneously. The simultaneous recording of two projections is indispensable to the study of premature beats, and in cases in which the morphology of the P-QRS-T loop is changing from cycle to cycle, but otherwise offers no important advantages over the recording of one projection at a time. If a time-delay screen having a pronounced afterglow is used the path traced by the luminous spot may be seen for several seconds. However, even this does not permit detailed study of the image, and it is preferable to employ a screen with minimal afterglow so that photographs with a clearly defined outline can be obtained. The simplest and most widely used practice is to obtain a still photograph of a single heart cycle with an exposure of one-fifth, one-half or one second, depending on the heart rate, and whether or not it is desired to photograph the P, QRS and T loops, or only a portion of the QRS loop. With practice it is possible to photograph the beginning of the QRS loop unobscured by the isoelectric spot and the P and T loops, or an automatic device can be set up to photograph the image at any instant during the P-QRS-T cycle.

*There is no relation between the X and Y co-ordinates of the oscilloscope, and the similarly designated co-ordinate axes of the body, X, Y and Z, which are defined as follows: X = transverse or horizontal axis, Y = sagittal axis, and Z = longitudinal or vertical axis.

Photographs obtained in this way on a stationary film register only a single cardiac cycle, or a part thereof, and therefore cannot be utilized to study the heart mechanism. One can accomplish this by photographing the continuous heart action on a slowly moving film.[9, 20]

Once photographs of the various projections are available, the negatives can be studied, or prints can be made. Stereopticon views are sometimes obtained by simple technics,[15, 24] but the most accurate representation of the spatial loop requires the construction of a wire model. This is tedious and is not suitable for routine use, being reserved for complex loops and for teaching.[16, 25] We obtain still photographs on 35-mm. film, which is placed in a suitable projector, the enlarged images being clearly delineated and convenient to study. If white paper is placed on the screen the trace can be reproduced with great accuracy. This is useful for both study and reproduction for publication.

Reference Systems

The cardiac vector is absolute, but unknown, and the preoccupation of the vectorcardiographer is concerned with attempts to define it as accurately as possible. This at once explains the multiplicity of reference systems, and the dissatisfaction with all of them. For all reference systems give but an approximation of the cardiac vector in man, whether one is concerned with vectorcardiography or electrocardiography, and the facts hardly justify any optimism that it will be otherwise in the predictable future.

A reference system may be defined as a fixed geometric figure delineated by a series of points on the surface of the body. Any pair of points defines a lead if electrodes are placed at these points and the difference of potential between them is measured. The function of the reference system is to find a true relation between the heart vector and the leads. It is supposed that the body, or a given plane of the body, fits the geometric construction selected and, therefore, that the leads obtained on a given geometric construction will yield the cardiac vector by more or less simple mathematical treatment. Burger and Van Milaan[26-28] have called attention to the fallacies in this approach and have branded as unscientific the a priori selection of a geometric figure. Furthermore, they point out that the heart is too large, in relation to the size of the trunk, for one to assume the existence of a single cardiac vector and that, moreover, the volume conductor is not homogeneous. They propose that mathematical formulas be derived from actual measurement of potential differences on the body surface as a first step and then that accurate geometric figures be constructed from these formulas.[26-28]

These investigators utilized a model of the human body, and an artificial heart, — that is, a known electromotive force (heart vector), — and were able to

demonstrate a linear relation between any lead and the rectangular components, X, Y, and Z, of the heart vector, as follows: lead = aX + bY + cZ. The coefficients, a, b, and c, are independent of the heart vector but are constant for a given lead. Unfortunately, they cannot be found in man, but they can be determined on the manikin, which is thus suitable for testing the accuracy of the different reference systems under controlled experimental conditions. Burger and Van Milaan performed such experiments and concluded that the equilateral triangle comes nearer to the truth than the rectangular systems and referred to it as the "lucky hit of Einthoven."

Because of the three-dimensional character of the cardiac vector it is necessary to register its projections in two or more planes to define its spatial position. A plane is derived from two leads in the manner described in the previous section; these consist in two unipolar leads,[18] one unipolar and one bipolar lead, or two bipolar leads. The last combination is the one most widely used. If the polarity of the reference system is so arranged that the positive terminus of the instantaneous vector is registered, the system is said to be one of positive polarity. This corresponds to that suggested by Einthoven, who represented the cardiac electromotive force by an arrow pointing in the minus-plus direction — that is, from active toward resting muscle. If the polarity of the system is so arranged that the negative terminus of the instantaneous vector is recorded, the system is said to be one of negative polarity.

The various geometric figures that have been proposed as reference systems are the equilateral triangle (or tetrahedron), and the tri-rectangular trihedron, or various modifications of these.[10, 12, 15, 16, 29, 30] Mann[6] was the first to use the Einthoven triangle to register the frontal-plane projection of the spatial vectors, and later Hollmann and Hollmann[11] and Wilson et al.[12] similarly utilized the equilateral triangle simultaneously and independently. Subsequently, Wilson and his co-workers[21] investigated the validity of Arrighi's sagittal plane, and this ultimately led to the concept of the equilateral tetrahedron, which became the basis for the reference system used by Conway, Cronvich and Burch,[14] and others, in their studies in vectorcardiography.

In the system used by Wilson[7, 12] standard Lead 1 was connected through an amplifier to the vertical set of deflecting plates, and the central terminal of Wilson and the left-leg electrode were connected to the horizontal set, and arranged so as to obtain a positive polarity. These two leads are parallel to the horizontal and vertical components of the cardiac vector, respectively, and their resultants from instant to instant, found by the oscilloscope, register the frontal projection of the spatial vector, as described above. Standardization is adjusted so that the vertical deflection is one and seven-tenths times as great as the horizontal projection for the same input. Thus, the cardiac electromotive force displaces the luminous spot through a horizontal distance proportional to E cos α, and through a vertical distance proportional to E sin α.* Although Wilson et al.[7, 12] did not record sagittal-plane projections in their vectorcardiographic studies, Wilson and his coworkers[21] confirmed Arrighi's observations that the Arrighi and standard limb leads give the same values for the vertical component of the cardiac vector.

Burch and his co-workers,[13, 14] basing their conclusions on Wilson's observations and extensive experiments of their own, constructed an equilateral tetrahedron as their spatial reference system. The apexes of their geometric figure are the shoulders, the pubis and the posterior point of Arrighi. They tested the validity of the equilateral tetrahedron by introducing a "dipole" into the esophagus of living subjects and then measuring the potential differences between the limb and back electrodes.[13] They concluded that the posterior point, which is located at the level of the seventh thoracic vertebra, 2 cm. to the left of the midline, is as electrically remote from a dipole in the region of the heart as the apexes of Einthoven's triangle. Thus, these investigators were able to record projections of the heart vector on a frontal and on a sagittal plane, and they adopted the polarity established by Einthoven.

In all orthogonal systems the component leads are parallel to the natural co-ordinate axes of the trunk and are mutually perpendicular. These features characterize the reference systems used by Schellong,[10, 15] Duchosal and Grosgurin,[32] Trocmé,[29] Sulzer and Duchosal,[33, 34] Grishman et al.[35] and ourselves. Duchosal and his collaborators[32-34] take great pains to identify the electrode positions of their reference system accurately, locating the center of the heart by fluoroscopic examination. Until recently, standardization corrections were made for inequalities in distances of the electrodes from the center of the heart imposed by the dimensions of the trunk. They employ a negative polarity.

The reference system almost exclusively in use in this laboratory at present is based on Duchosal's system as modified by Grishman et al.[35] The thorax, compared to various geometric figures, most closely resembles a rectangular parallelopiped, and on it are placed four standard electrodes, which serve as the basis for three orthogonal bipolar leads. The right-arm lead wire (RA) is connected to an electrode on the right posterior axillary line at the level of the scapular spine, the left-arm lead wire (LA) to an electrode in the right posterior axillary line at the level of the posterior superior iliac spine, corresponding approximately to the level of the second

*α = angle between manifest vector and line of Lead 1.

lumbar vertebra, and the left-leg lead wire (LL) is attached to an electrode in the right anterior axillary line at the same level as the lower posterior electrode. The C lead wire is attached to an electrode in the left posterior axillary line at the same level as its opposite number (LA) on the right. The appropriate combinations of these yield the three leads, X, Y and Z, and the three planes designated horizontal, sagittal and coronal (frontal), as follows:

Lead X = C − LA; Lead Y = LL − LA; Lead Z = LA − RA;
Horizontal projection = C − LA on X axis, and LL − LA on Y axis, of oscilloscope;
Sagittal projection = LL − LA on X axis, and LA−RA on Y axis, of oscilloscope;
Coronal projection = C − LA on X axis, and LA − RA on Y axis, of oscilloscope.

Lamb and Dimond[26, 27] recently advocated a reference system combining both basic systems, and differing from them in that the two leads, which are used simultaneously to obtain a given projection of the spatial vectors, are not in the same plane. They utilized three leads: a frontal lead (Einthoven's Lead 1), a sagittal lead, composed of a negative electrode on the right arm and a positive electrode in the right mid-axillary line at the level of the second lumbar vertebra, and a horizontal lead, consisting of a positive electrode in the midline over the second lumbar vertebra and a negative electrode just above the umbilicus.*

There are many other modifications of the two basic reference systems, but those described in detail were selected as representative examples. Each author of a system, or a modification thereof, has claimed superiority for his creation, and not without some justification. For although the ideal reference system is Utopian and only an approximation of the true cardiac vector is attainable, for reasons stated above, each system has advantages over others in certain persons and under certain conditions. Theoretical or actual comparisons of the different systems simply emphasize the shortcomings of all reference systems and not the unqualified superiority of any one of them.[16, 25, 26, 28-40]

The advantages claimed for the equilateral tetrahedron are that it employs the Einthoven triangle, and that the posterior point is remote from the center of the heart. Duchosal claimed remoteness of the electrode positions in his system, and simplicity of the geometric figure. Without sacrificing any of its advantages, the reference system employed by Grishman, and by us, is much more practical and easier to use, and its positive polarity is in keeping with the time-honored practice advocated by Einthoven. Lamb and Dimond consider their modification superior to others because the angles to the force measured subtended by the electrodes are equal, and as great as the body will accommodate without violating the distance necessary for remoteness. Compared to other systems the chief difference found by them was in the anteroposterior electromotive force, which invariably was greater with their system of electrode placement.

The angles to the force measured subtended by the electrodes is never known in man, the most distant points on the trunk are never remote enough to warrant the assumption that there is a single cardiac vector and the volume conductor is not homogeneous. Even so, if the coefficients for various leads were known, one lead would be as good as another, every reference system would be satisfactory, and the standardization of instruments would include the proportionality factor of the coefficient. This is the dream of the physicist.[25]

Interpretation of Vectorcardiograms

The interpretation of vectorcardiograms is based on the spatial direction and magnitude of the instantaneous vectors, the general spatial disposition and shape of the loops as a whole, the direction and speed of inscription and the relation between the QRS and T loops. With experience the spatial characteristics of vectors can be visualized from inspection of the recorded projections, provided two or more planes are available. Duchosal recommends that three planes be utilized when one is studying the initial QRS vectors, since a spatial vector, which is perpendicular to a plane and therefore not recorded in that plane, will be overlooked if only two projections are obtained.[16] The direction and magnitude of the instantaneous vectors can be quantitatively described in relation to the natural co-ordinate system of the body and the one-millivolt standardization deflection, respectively. This is not done routinely, however, since the relation of the instantaneous vectors to each other is more important than their absolute values.

The spatial position of the loops, like that of the instantaneous vectors, can be described in terms of the natural co-ordinate system of the body, or in relation to each other. Their morphology varies from a smooth ellipsoid or circular figure to complex and irregular forms difficult to describe. The direction of inscription in the more regular curves can be described as clockwise, counterclockwise[7] or figure-of-eight. The speed of inscription of the loops is determined by the distance between time markings, closely spaced intervals indicating a gradual change in direction and magnitude of successive resultants, and widely spaced intervals signifying a rapid change from instant to instant. Close spacing of the time markings is significant only when displayed in all three projections; its occurrence in a single plane will result from the

*These three leads are designated by other authors as horizontal, vertical and sagittal, respectively.

perpendicular relation of the vectors to that plane. The time markings are also used to measure the duration of the loop, and to identify comparative points in different projections.

Normal Vectorcardiogram

Three loops can be recognized in the vectorcardiogram, representing auricular depolarization, ventricular depolarization and ventricular repolarization, designated, respectively, as the P, QRS and T loops, or as PsÊ, QRSsÊ, and TsÊ loops in their spatial constructions. Vectors corresponding to atrial repolarization have not been identified (Fig. 2).

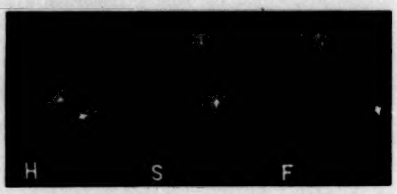


FIGURE 2. *Vectorcardiogram from a Normal Twenty-Six-Year-Old Man.*

H = horizontal, S = sagittal, and F = coronal (frontal) projection. The white spot is the O point. The largest loop in each projection is the QRS loop. The T loops are clearly seen in all three planes, enclosed by the QRS loops. The P loop is obscured by the T loop in the H and S projections but is visible in the F projection as the smallest of the three loops. Arrows indicate direction of inscription of QRS loops. Intensity modulation is 400 cycles per second.

The PsÊ Loop

This part of the vectorcardiogram has been largely neglected, probably owing to the technical difficulties of recording it unobscured by the larger QRS and T loops. Duchosal published several P loops without mentioning any specific characteristics.[16] Conway et al.[14] described the P loop as small and irregular, or mitten shaped, as being slowly inscribed and as occupying a position more or less parallel to the QRS loop. We have confirmed these findings, and have frequently noted that the P loop is rather elongated.

The QRSsÊ Loop

The largest of the three loops is the QRS loop, which is described as being narrow, smooth and ellipsoid[9, 14-16, 41] or as having flat indentations.[15] The initial and terminal parts of the loop are inscribed slowly, and the remainder more rapidly. The loop begins and ends at the same point (O point) and is therefore "closed." We have occasionally observed "open" loops in otherwise normal vectorcardiograms, but these have not been reported by others.

The spatial position of the QRS loop varies with age, body position and respiration. According to Lamb and Dimond[37] the QRS loop has an extreme rightward and posterior position during the first week of life, but assumes a more anterior and less rightward position in older children, ultimately becoming vertical and inferior.* They state, without giving any criteria, that there is clockwise rotation after the first week of life. Scherlis, Lasser and Grishman[41] observed that the QRS loop became progressively more horizontal and posterior with advancing age, and gave as the normal range 0° to +85° in the frontal plane and +35° to −45° in the horizontal plane. They also noted that the QRS loop assumed a more vertical and anterior direction during inspiration and in the upright position, and an opposite direction during expiration and in the recumbent position. Schellong[15] gave 45°± as the normal position of the QRS loop in the frontal plane, and Conway et al.[14] considered the normal spatial position as anterior (100° in their polarity system), downward and to the left (+65°), with 45° clockwise rotation. The wide variation noted by different observers is probably due to the small number of cases studied and the different reference systems employed. Duchosal and Sulzer[16] state that the spatial position of the QRS loop is the same as the anatomic axis of the heart, but offer no supporting evidence. These observers found that the largest QRS vectors occur 0.03 to 0.045 second after the onset of the QRS loop.

There is general agreement that the normal QRS loop is inscribed in a counterclockwise direction in the horizontal, and in a clockwise direction in the sagittal projection. As a rule the frontal loop is inscribed in a clockwise direction.[9, 14-16, 41, 42] The initial vectors are small and point to the right, anteriorly and superiorly. The initial vectors, the general disposition of the whole loop and the direction of inscription may be altered by position and rotation of the heart. As shown below, these may also be altered by myocardial infarction, chamber hypertrophy and intraventricular conduction defects. We have studied the effect of position and rotation of the heart by an experimental method and have observed striking alterations in the initial vectors with positional changes; the horizontal and sagittal projections are always inscribed in a counterclockwise and clockwise direction, respectively, whereas the frontal projection varies considerably with position and rotation of the heart.[42]

The TsÊ Loop

The T loop is about one fifth the size of the QRS loop, and is inscribed more slowly than the QRS loop, especially its centrifugal limb.[14] It is usually described as ellipsoid, and its position in relation to the QRS loop is constant.[14-16, 41] Schellong[15] noted that the T loop is usually enclosed by the QRS loop, but considered the parallelism between the

*See previous section for polarity.

terminal QRS vectors and the centripetal limb of the T loop to be the most constant relation, the widest divergence being 45°. Duchosal and Sulzer,[16] Conway et al.[14] and Scherlis, Lasser and Grishman[41] observed that the QRSsÊ and TsÊ loops as a whole were parallel within a range of 0° to 30°. The spatial position of the TsÊ loop is somewhat anterior, inferior and to the right of the QRSsÊ loop. Conway, Cronvich and Burch[14] and Schellong[15] noted that the direction of inscription of the T loop was the same as that of the QRS loop. Others have found it difficult to define the direction of inscription of the normal T loop, since it is prone to cross its own path several times.[43, 44]

Derivation of Electrocardiographic Leads from the Vectorcardiogram

The three factors that must be considered in defining the relation between electrocardiographic leads and the vectorcardiogram are the spatial position of the cardiac vector, the lead axis — that is, the spatial relation between the electrocardiographic lead and the cardiac vector — and the distance of the lead site from the cardiac vector.[32]

Duchosal et al.[45] suggested that the limb leads were related to the frontal-plane projection, the precordial leads to the horizontal-plane projection, and the esophageal and intracardiac leads to the sagittal-plane projection, and they reported many examples of leads so derived. Scherlis, Lasser and Grishman[41] followed this suggestion and placed the frontal loop in the triaxial reference system of Bayley so that the point of origin of the loop coincided with the intersection of the axes, and then derived the limb leads (standard and unipolar), as Duchosal did, by noting the disposition of the loop on the positive or negative poles of the lead axes and the order and rate of inscription of the loop. The projection of the loop, point after point, on the positive or negative side of the lead axis reproduces the P, QRS and T complexes.

In the example shown in Figure 3 the initial forces are on the negative side of Lead 1 and are small; therefore, a small Q wave is derived. The following vectors for a brief interval are perpendicular to Lead 1, and their projection on this lead is 0, resulting in an isoelectric interval. A moderate R wave is then derived, since the projections of succeeding portions of the loop fall on the positive half of the Lead 1 axis and are of moderate magnitude. Finally, the projections of the terminal part of the QRS loop fall on the negative part of Lead 1 and are small, resulting in a small S deflection. The projections of the T vectors fall on the positive side of the Lead 1 axis, but are almost perpendicular to it. Accordingly, the T wave is upright but low. The ST segments are derived in the same manner as the QRS and T deflections; they are isoelectric when the QRS loop is closed, and deviated from the base line when the QRS loop is open. The direction of deviation, like that of the other deflections, is determined by the relation of the open end of the QRS loop to the positive or negative half of the lead axis.

The other limb leads, and the precordial leads, can be derived in a similar manner, the horizontal loop being utilized for the latter. The horizontal projection is superimposed on a diagrammatic cross section of the thorax, the point of origin of the loop being in the center of the section, or just to the left of center. All precordial leads are derived at a single level, unlike the conventional practice of registering the precordial leads at different levels.

Leads derived from loops, and those actually recorded, may or may not be identical — that is,

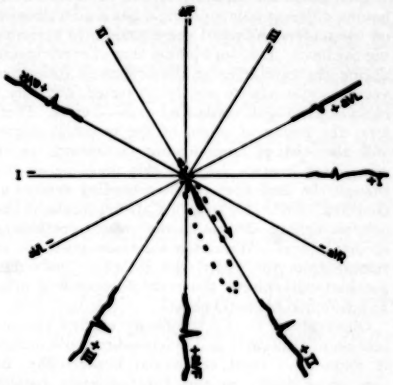


Figure 3. *Derivation of Limb Leads from Coronal Projection Reproduced from Figure 2 (See Text).*

the vectorcardiogram and electrocardiogram may be concordant or discordant. This feature can be predicted from the electrocardiogram alone. If leads on the opposite ends of an axis (for example, V_6 and V_6R) are compared and one is the mirror image of the other, concordance may be assumed to exist; if one is not the mirror image of the other, discordance may be assumed to exist.[32, 45] Grosgurin and Duchosal[46] believe that discordance in relation to the precordial leads is especially common in hypertrophy of the right ventricle, and they elaborate a theory of multiple or moving points of origin of resultant vectors to explain this phenomenon. Although we disagree with their conclusions, we consider their contributions on this subject to be of fundamental importance.

At any instant during the cardiac cycle the overall resultant depends on the directions and magni-

tudes of the component vectors. The apparent point of origin of the resultant vector, however, depends not only on the directions and magnitudes of the component vectors, but in addition on their points of origin and on the lead site. Therefore, the point of origin appears to move when the lead position is changed, and, concomitantly, the direction and magnitude of the resultant vector appear to change, although the actual values must remain unaltered regardless of the electrode site. Conversely, even though the electrode site remains constant, the apparent point of origin of successive resultants will appear to change, because the component vectors themselves change from instant to instant. Grosgurin and Duchosal[25, 46] believe that this apparent movement or multifocal origin of the cardiac vector is the explanation of discordance.

This geometric analysis of two or more vectors having different points of origin has a direct bearing on the understanding of the electric field surrounding the heart. It is our opinion that at every instant during the cardiac cycle the origins of component vectors are in reality widely separated, not only in cases displaying discordance but in all cases. Therefore, the points of origin of the resultant vectors will also change from instant to instant, as the component vectors do, and this must be so even though the lead sites of the recording system are constant. Since this situation always exists, it does not, we believe, determine the presence or absence of discordance. When the electrode positions are remote from the heart, the recording instrument automatically places the multiple points of origin at a common point (O point).

Observations in this laboratory confirm the contention of Grosgurin and Duchosal that discordance is common in right ventricular hypertrophy, but cast some doubt on the direct relation between them.[47] Rather, a relation appears to exist between vertical or extreme horizontal heart positions and discordance in the precordial leads.[47] The explanation for this may be found in the equation: Lead = $aX + bY + cZ$. A lead value derived from two of the components — for example, X and Y — will be true only when the third component — in this instance, Z — is small in relation to X and Y, assuming that the coefficients are of the same order of magnitude. Conversely, if such a relation of Z to X and Y does not exist, a large error will be introduced by neglect of Z. Consequently, leads derived from a single planar projection, which necessarily incorporates but two of the three components of the heart vector, will be similar to recorded leads only when the third and "unrepresented" component is relatively small, but not when it is large. Thus, discordance in relation to precordial leads will be observed when forces parallel to the Z co-ordinate are large, as in vertical or extreme horizontal heart positions. Nevertheless, even under these conditions, discordance will not exist if the precordial leads are obtained at a level where the vertical forces have a zero potential (O point). This level can be determined by extensive exploration of the trunk.

Discordance between limb leads and the frontal projection occurs when the component of the cardiac vector parallel to the Y co-ordinate is large in comparison to the other two components, X and Z.

There is a fallacy, therefore, in the derivation of scalar leads from a single planar projection of the spatial vectorcardiogram. It is a fundamental principle that each lead on the surface of, or within, the body has a spatial orientation in relation to the electric field surrounding the heart. When this principle is not neglected, discordance in the sense defined by Grosgurin and Duchosal does not exist. However, differences between derived and recorded leads are observed in all cases. The factors responsible for these discrepancies are errors inherent in the vectorcardiographic method, the heterogeneity of the conducting medium, and the inequality of distances between various electrode positions and the electric center of the heart, as well as the lack of remoteness of some electrode positions.[27]

The errors inherent in the vectorcardiographic method, discussed above, consist chiefly in the unpredictable variations between the ideal axes of the natural co-ordinate system and the arbitrary lead axes of the reference systems. The variations in conductivity of different tissues, especially in relation to electrode placement of the vectorcardiographic reference systems and unipolar precordial leads, undoubtedly play a part in the lack of similarity between recorded and derived leads. Furthermore, distance of electrodes from the heart is important, especially in relation to the so-called semidirect precordial leads, which are close enough to the heart to be influenced by specific portions of the cardiac field. Grant and Estes[48] have denied the validity of the last two factors, but Burger and Van Milaan[27] and Wilson et al.[49] have demonstrated their importance.

In summary, the cardiac vector, in being recorded, is modified by the nature of the conducting medium and the recording system used. These modifying factors have different influences on the vectorcardiogram and electrocardiogram, and herein lies true discordance. The gross differences between derived and recorded leads observed by Grosgurin and Duchosal, defined by them as discordance, are dependent on the method of deriving scalar leads from a single planar projection of the spatial vectorcardiogram, thereby neglecting one of the three components of the cardiac vector.

(To be concluded)

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MEDICAL INTELLIGENCE

PERFORATION OF THE AORTA BY BENIGN ESOPHAGEAL ULCER*

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SPONTANEOUS perforation of the aorta by a benign esophageal ulcer has not been reported. As a surgical complication such a perforation has been described in 3 cases. Merindino and Emerson[1] presented 2 cases in which aortoesophagogastric fistula followed resection for esophageal carcinoma. In 1, a misplaced suture passed through the aortic media. In the other, separation of the suture line resulted in an abscess followed by an aortoesophagogastric fistula with fatal hemorrhage ten months after operation.

Malignant ulcers commonly invade the aorta, with fatal consequences. Knaut[2] found a total of 34 cases in 1896. Carr and Hanford[3] added 18 cases through 1922. In 1946 Postoloff and Cannon[4] found 6 additional cases and added 2 of their own, bringing the total reported cases of perforation of the aorta by esophageal carcinoma to 50.

Postoloff and Cannon[4] studied the pathogenesis of this condition with considerable care and advanced the theory that perforation resulted from interference with the blood supply of the aorta secondary to thrombosis of the vasa vasorum and not from invasion of the entire vessel wall by tumor and not from bacterial infection. In their experience, the only part of the aorta invaded by tumor was the adventitia, the media and intima being spared.

Benedict and Sweet[5] found a benign esophageal ulcer associated with duodenal ulcer and hiatus hernia in 6 of 60 patients with benign stricture of the esophagus. In the case reported below, shortly after the perforation of a duodenal ulcer, a penetrating ulcer of the esophagus contained within a large hiatus hernia eroded the wall of the aorta, resulting in sudden death.

CASE REPORT

Mrs. E. F., a 63-year-old woman, was admitted to the Emergency Ward of the Massachusetts General Hospital on October 3, 1951, complaining of pain, indigestion and heartburn of 6 months' duration.

Twelve years before admission she had begun to have intermittent attacks of indigestion and heartburn associated with a sensation of fullness in the middle of the chest. Because of the persistence of the symptoms, she was admitted to another hospital, where x-ray examination showed an inoperable carcinoma of the stomach. At the time of discharge she was placed on a bland diet and thereafter remained asymptomatic for 5 years. Four years before admission she became jaundiced. At the same time the heartburn and indigestion recurred, only to subside with the disappearance of the jaundice over a period of several weeks. Six months before admission, the attacks recurred, and along with the dyspepsia she first noted a chronic productive cough, which continued until admission. Two weeks before admission the abdominal distress became much more severe and was no longer relieved by sodium bicarbonate. She became anorexic and acutely ill; great pain developed.

Physical examination revealed a dehydrated woman in acute distress. Dullness and absent breath sounds were present over the left lower portion of the chest. There was tenderness over the same area, with spasm and tenderness of the upper abdomen.

Examination of the blood showed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 16,700, with 86 per cent neutrophils. The urine was normal.

X-ray examination demonstrated fluid in the left pleural space and a questionable area of consolidation in the left lower lobe.

A chest tap in the 10th intercostal space yielded 400 cc. of pus and air. On the following day the left subphrenic space was explored and drained under local anesthesia, and a tentative diagnosis of perforated duodenal ulcer was made. When the patient's condition had improved somewhat, gastrointestinal studies revealed a greatly dilated stomach with pyloric obstruction. She was then placed on constant gastric suction, with a jejunostomy for feeding.

On November 9 laparotomy confirmed the diagnosis of perforated ulcer, and an anterior gastroenterostomy was done. She seemed to do well until 28 hours after operation, when she became restless and extremely apprehensive, vomited a large amount of bright-red blood and died suddenly.

Autopsy disclosed a large hiatus hernia measuring 10 cm. in diameter. Within the hernia the esophagus was filled with bloody, mucoid fluid; 3 cm. above the cardia in the esophagus was a rent, 0.6 by 0.1 cm., at the center of an ulcer measuring 1 by 1.5 cm. At the center of the rent there was a communication with the thoracic aorta, which was adherent at that point.

DISCUSSION

In retrospect, the x-ray examination five years before death probably revealed a hiatus hernia that was misinterpreted as a gastric cancer.

In view of the theory of Postoloff and Cannon[4] that aortic perforation results from thrombosis of the vasa vasorum one may speculate on the cause of the perforation in the case reported above. Since no periesophageal abscess was found, a prior perforation of the esophagus with secondary aortic erosion did not occur, nor did sepsis from the duodenal perforation play a part. The inflammatory changes must have resulted from the contiguity of the esophageal ulcer and the aorta. The pressure of the hiatus hernia may have provided such a contact, being the primary factor in the fatal perforation.

SUMMARY

A case of perforation of the aorta by a benign esophageal ulcer, with fatal hemorrhage, is reported. Though such perforations secondary to malignant ulcer are not uncommon, spontaneous esophagoaortic fistula secondary to a peptic ulcer of the esophagus has not previously been reported. The pathogenesis of this complication is understandable in the light of pathological studies on perfora-

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tion of the aorta by esophageal carcinoma, as well as the anatomic findings in the patient.

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DOCTORS AFIELD

Mark Hopkins: Physician, Educator

Dana L. Farnsworth, M.D.*

CAMBRIDGE, MASSACHUSETTS

In July, 1829, a young man of twenty-seven received his M.D. degree from the Berkshire Medical Institution in Pittsfield, Massachusetts. In a letter to his brother he stated:

> I have sent my dissertation for M.D. to Pittsfield, and I am glad it is the last thing of the kind I shall ever be obliged to write. I have also to pay them $15. and my tuition here, and then I shall be through with that — but as Stephen Tucker said of the beans, before you get through with one hill, another comes. I begin already to enjoy some of the pleasures of a Dr.'s life in being called up nights, &, &.[1]

In a short while he opened an office in New York City at 53 Charlton Street. He thought it was a pleasant office, and he wanted to have it furnished well, but for the sake of economy, he had to have a sofa bedstead so that he could sleep there. However, patients did not come, and in a few weeks he moved to 79 Grand Street, but still the patients did not appear. By March, 1830, he confided to his brother that he still had no practice and saw no prospects of any. He thought that if he could live there for four or five years, he might acquire a practice, but this he could not afford. After waiting until July, 1830, he gave it up and went into partnership with Dr. Silas West, of Binghamton, New York. His stay there was much shorter, because in September, 1830, he was elected professor of moral philosophy and rhetoric at Williams College. The young man was Mark Hopkins, and this appointment marked the beginning of fifty-seven years of teaching at Williams.

Mark Hopkins was born at Stockbridge, Massachusetts, in 1802, being a member of a well established family in that community.[2] His great-uncle was Ephraim Williams, the founder of Williams College. He himself graduated from Williams in 1824 and served as tutor for the next three years. It was probably the favorable impression he made on the college authorities and on the students that led to his appointment to a professorship in 1830.

From the time he began his formal teaching at Williams, he abandoned all thought of practicing medicine, though the influence of his education was evident in various ways. He always insisted that some knowledge of anatomy and physiology should be part of the general education of college students. For his lectures in these subjects he bought a large model or manikin at a cost of $600, but since the college had no money to pay for it, he signed a note for it and started to earn the money by giving lectures in the neighboring towns.

Some idea of his concept of medicine can be gained from his comments to a medical class at Pittsfield in 1840.[3] He admitted that he had not kept up with medicine and that many new discoveries had made him feel out-of-date. He deplored the tendency of physicians to consider the domain of medicine as solely their own, and he thought that the public generally should have a considerable knowledge of the laws of health, for this was its only guard "against the prevalence of quackery, which is found to deposit its eggs and mature its growth upon ignorance alone." In his opinion the profession always had been and probably always would be, next to that of politics, the favorite resort of quacks. He said that the study of medicine is pleasant, but that the practice often leads to great perplexity and trial of the feelings.

For the young physician, he considered the qualities of mind that should be cultivated to include the constant exercise of judgment founded on observation. He would next encourage the powers of reflection and generalization. He strongly recommended that each physician should have a feeling of heartfelt interest in his patients. In addition, he thought each physician should be able to express himself in public as well as in writing.

He considered it the business of the whole community to see that physicians received proper education; it ought to encourage and sustain institutions necessary for their full education. He thought that physicians should be well versed in knowledge outside the field of medicine.

Six years after he was appointed a professor he was made president of Williams College. His inaugural address is the first surviving document that throws unmistakable light on the reasons for his great reputation as a teacher.[4] He considered education of much greater import than the mere acquisition of factual learning. For him, education consisted of influences that might be brought to bear upon the mind in indirect ways, and then of direct instruction itself. He considered the former much the more important: "Instruction may form

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the intellect; influence molds the moral character." He believed that there were some schools in the country in which the real interests and progress of the pupils were sacrificed to their appearance at examination. He thought that a really good mind should not be pushed too fast. In his opinion every man who was educated at all was, of necessity, self-educated. The excellence of an instructor consisted not in his amount of knowledge, nor yet his facility of communication:

> [It lies] in his power to give an impulse to the minds of his pupils and to induce them to labor. For this purpose nothing is so necessary as a disinterested devotion to the work, and a certain enthusiasm which may act by sympathy on the minds of the young.

In this address he defines his system of education. It regards man as possessed of a body, which is to be kept in health and vigor, and of intellectual faculties, whose object is truth. It considers man as having faculties whose object is beauty and, lastly, as possessed of a moral nature, whose purpose is goodness. In summary he states that this system will form minds to the love and pursuit of truth, beauty and goodness.

He deplores the common attitude that faculty and students are opposite parties with opposing interests. He considers it absolutely necessary for good education that the students and faculty have a common object. A student who does not have this feeling should not be in the institution.

Although he was very popular with students and immensely respected by his faculty, he was not without his critics. The criticisms were not directed at him personally, but were based on the conflicting philosophies of education that were held by some of his faculty members.

In 1868 Williams College had a rebellion in which the students unanimously severed their connections with the college, because the faculty had passed a rule requiring strict attendance at all classes or making up any work missed if absence was required. On the face of it, this looked like an unreasonable development; actually, it was a complicated maneuver in the struggle between the two rival philosophies of education. One of these was the strict authoritarian imparting of information; the other was that of President Hopkins.

The rebellion occurred during an extended absence of President Hopkins, who was on a speaking tour. On his return it was immediately and diplomatically suppressed by him without much criticism, from either the faculty or the students, and all the students returned to college. One of the chief critics of the President, Professor Carter, who himself was to be president of the college later, said that Dr. Hopkins was not a believer in rigid rules, and thought a personal and flexible system of student government was desirable. He thought rigid and minute rules engendered antagonism, considering kindly and patient example to be of much greater worth than formal restrictions. He was opposed to any definite system of penalties. It was offensive to his ideas of proper training to treat all students in exactly the same way, since they were not alike in tendencies, training or abilities.

As his fame spread, he became in great demand as a lecturer. He gave four series of Lowell Lectures in Boston. Early in his career he received honorary degrees from Dartmouth, Harvard and the University of New York, and then at the end of his career, Harvard conferred upon him a second honorary degree, that of Doctor of Laws.[5]

In 1872 he resigned the office of President, both because of his age of seventy and to forestall possible suggestions that he retire. He retained his professorship and continued his teaching until his death in 1887. As President Carter has said, "He was mature when he was young and young when he was old."[6]

"The ideal college is Mark Hopkins on the one end of the log and the student on the other." Through this statement, attributed to President Garfield, Mark Hopkins is most widely known by the general public. The interesting point is that there is no evidence that President Garfield ever made the statement in this form.[7] The so-called quotation had its origin in a protest meeting at Delmonico's Restaurant in New York City over the lax methods of administration of Mark Hopkins at Williams. After the president's critics had had their say, Garfield, then an attorney in New York, made an impassioned defense of his president. No written account exists of what he actually said, but others attending the meeting remembered various versions of his remark, none of them alike and none mentioning the log. It was not until 1891, twenty-three years after the original remark, that a Williams alumnus, John Joseph Ingalls, who had become a Kansas politician, made a strongly emotional speech in which he discussed President Garfield and his interest in Mark Hopkins. In the course of his speech he attributed to Garfield the statement, "A pine log with the student at one end and Dr. Hopkins at the other would be a liberal education." Thus the so-called quotation evolved, and Mark Hopkins achieved a permanent place in educational folklore.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39191

PRESENTATION OF CASE

A forty-seven-year-old woman was admitted to the hospital because of enlargement of the parotid glands.

The swellings had been present for over a year but because of the absence of any symptoms, the patient had not consulted a physician until eight months before entry, when weakness developed. At that time the swellings were investigated by x-ray examination, but no duct calculi were found; the patient did not consult her physician again about them since the weakness cleared up after she had taken some pills. Three weeks before admission she noticed burning of the mouth after eating, which became progressively worse, as did dryness of the mouth. The gums did not bleed, but her dentist told her that her teeth were becoming soft. Recently she had noticed puffiness about the eyes but no increased or decreased lacrimation, and no pain.

Three years before entry a left simple mastectomy was done for a lesion said not to have been carcinoma. She denied ever having had rheumatic fever or scarlet fever.

Physical examination revealed a well developed and well nourished women in no acute distress. There was bilateral puffiness of both upper eyelids. There were bilateral, diffuse, moderately firm, nontender parotid swellings measuring about 5 by 6 cm. The tongue was coated, but the mucosa was not especially atrophic. The lungs were clear. A Grade 2 systolic murmur was present over the apex and base, and the aortic second sound equaled the pulmonic. The rest of the examination was negative.

The temperature was 99.2°F., the pulse 70, and the respirations 18. The blood pressure was 140 systolic, 80 diastolic.

The urine had a specific gravity of 1.010 and gave a ++++ test for albumin; the sediment contained 20 red cells, 8 white cells, frequent hyaline casts and an occasional cellular cast per high-power field. A urine culture was negative. A urine concentration test revealed no specific gravity above 1.010. Examination of the blood showed a hemoglobin of 10.9 gm. and a white-cell count of 5700, with 72 per cent neutrophils, 22 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The clotting time was normal; the hematocrit was 27 per cent. The red cells and platelets were normal on the smear. A bone-marrow aspiration demonstrated no abnormality. The sedimentation rate was 56 mm. in one hour. The nonprotein nitrogen was 32 mg., the cholesterol 207 mg., the amylase 32 units, the alkaline phosphatase 1.8 units, the total protein 5.06 gm., the albumin 3.18 gm., the globulin 1.88 gm., the calcium 8.4 mg., and the phosphorus 4.8 mg. per 100 cc.; the sodium was 134.2 milliequiv., the chloride 106 milliequiv., the potassium 6.2 milliequiv., and the carbon dioxide 22.4 milliequiv. per liter. A glucose tolerance test gave the following readings: fasting blood sugar, 104 mg.; half an hour after glucose 171 mg., after one hour, 145 mg., and after two hours, 152 mg. per 100 cc. The prothrombin time was 20 seconds (normal, 17 seconds). An electrocardiogram was normal. A roentgenogram of the chest disclosed the heart shadow to be at the upper limits of normal, but examination was otherwise negative. A gastrointestinal series was negative. On intravenous pyelogram, the kidneys were poorly visualized. Both kidneys excreted the contrast substance promptly but in greatly diminished concentration. The upper urinary passages were inadequately visualized.

In the hospital the patient showed little immediate change clinically although the urine continued to give a ++ to ++++ test for albumin and the sediment contained many red cells. An ophthalmologist found moderate chemosis of the eyelids and normal disks, fundi and vessels. The lachrymal glands were not enlarged; a Schirmer test revealed a definite impairment of tear flow. Vision was unimpaired. An otolaryngologist found dryness and crusting of the nasal mucosa and dryness of the mucous membrane of the mouth. No secretion could be expressed from the ducts of the parotid or submaxillary glands.

On the tenth hospital day the serum nonprotein nitrogen was 66 mg. per 100 cc. Five days later the patient suddenly began to have projectile vomiting, and two hours later had a convulsion, with biting of the tongue and urinary incontinence, that lasted seven minutes. Examination showed her to be oriented but apathetic. There was a uremic odor to the breath. There were dullness and diminished breath sounds to the tip of the scapula on the right, a normal abdomen and ++ sacral edema.

A few minutes later the patient complained of "feeling funny" and five minutes later became unresponsive. Twitching of the abdominal wall ap-

peared and then clonic motion of the right arm and to a lesser extent of the right leg. This was followed by a generalized convulsion for one minute and then five minutes of postconvulsive unresponsiveness. Subsequent examination showed no definite facial weakness or inability to move the arm. The knee and ankle jerks were quite brisk, more so on the right. The plantar reflex was extensor on the right and questionably flexor on the left. Later in the day the patient was confused, and when being tested for visual acuity, she gave inconsistent replies. Confrontation fields were equal bilaterally; nystagmus was present on gaze to the right but was not marked nor consistent; the pupils reacted briskly, and the disks were not choked. There was a small fresh hemorrhage in the vitreum of the right eye. Still later in the day a diffuse petechial rash appeared on the face, and there were purpuric areas on the arm. A lumbar puncture showed an initial spinal-fluid pressure equivalent to 285 mm. of water, and a pressure after the removal of 30 cc. of fluid equivalent to 175 mm. The spinal fluid was clear and colorless, with only a faint ground-glass quality, contained 81 red cells per cubic millimeter, and 57 mg. per 100 cc. of protein, and gave a normal gold-sol curve. On the same day a urine specimen had a specific gravity of 1.018, and gave a ++ test for albumin; the sediment contained 150 red cells, 8 white cells and ++ bacteria per high-power field. The serum nonprotein nitrogen was 100 mg. per 100 cc., and the sodium 143.3 milliequiv., the chloride 107 milliequiv., the potassium 4.4 milliequiv., and the carbon dioxide 10.4 milliequiv. per liter. The patient was treated with Dilantin, and on the following day she was oriented although she slept much of the time. Ophthalmologic examination showed no new findings. Vision was normal, the fields were full by confrontation, and there was no nystagmus. There were no further seizures. Two days later the serum nonprotein nitrogen was 80 mg. per 100 cc., and the sodium 114.0 milliequiv., and the carbon dioxide 17.4 milliequiv. per liter. She was given dextrose and saline solution intravenously, but on the following day the nonprotein nitrogen was 100 mg. per 100 cc., and the sodium 110.5 milliequiv., and the chloride 90 milliequiv. per liter. Four days later, after further sodium chloride administration, the serum sodium was 134.2 milliequiv. per liter.

During the next week the patient was fairly comfortable, although troubled with nausea. There was generalized puffiness; purpura was more marked than before, and the abdomen was markedly distended but not tender. The temperature showed elevations to 101°F.; the blood pressure was about 200 systolic, 100 diastolic. She gradually became more oliguric. The urine gave a ++++ test for albumin, and the sediment was loaded with red cells and obtained frequent granular casts. She was given 50 mg. of cortisone by mouth every four hours but showed only questionable improvement. Oliguria persisted. The serum nonprotein nitrogen was 150 mg. per 100 cc., and the sodium 127.5 milliequiv., the potassium 5.6 milliequiv., and the carbon dioxide 11.8 milliequiv. per liter. Nausea, peripheral edema and signs of pulmonary edema became severe. Gradually, the patient became more somnolent and weaker. The blood hemoglobin fell to 5.2 gm. per 100 cc., the platelets were decreased in number to 40,000 per cubic millimeter, and the red cells showed considerable variation in size and shape. Many red cells were stippled. The white-cell count varied during this period from 4700 to 13,700, with a neutrophil count of 81 to 93 per cent. There was no eosinophilia. Transfusions were given, but the nonprotein nitrogen remained elevated and the blood hemoglobin fell to 2.6 gm. per 100 cc. After being semistuporous for about a week the patient died on the fifty-seventh hospital day.

Differential Diagnosis

Dr. Alfred Kranes*: Dr. Heath, can you tell us what a Schirmer test is?

Dr. Parker Heath: A standard-sized strip of filter paper is put in the conjunctival sac, and the lid is closed over it; then at intervals of five, ten and fifteen minutes readings are made to see how much moisture the paper has absorbed; normally, it is saturated after ten to fifteen minutes. This patient did not show any moisture.

Dr. Kranes: There was no tearing, indicating decreased lacrimal function.

I approach a problem of this sort with considerable misgiving, because it has long been my opinion that any attempt to predict what the microscopical sections will show in cases of renal insufficiency is one of the less fruitful medical exercises. Some time ago I asked Dr. Castleman to refrain from asking me to discuss such problems, but apparently he is still trying to sharpen my diagnostic acumen.

I can begin safely enough by stating that the patient had Mikulicz's syndrome and that she also had diffuse renal disease. Whether I can tie these two together is another question. I shall also begin by assuming that these two disturbances were independent of each other, although that may not turn out to have been so. Of the types of renal disease that can give this picture, the most serious consideration must be given to subacute glomerulonephritis, which would explain most of what was found in this patient. It would explain the urinary findings, the blood findings and the electrolyte abnormalities, as would any type of renal disease for that matter; it would also explain the hypertension, the terminal pulmonary edema and the purpura. Purpura is not too uncommon a terminal finding in patients with glomerulonephritis although in those I have seen, it has more often been confined to the lower

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half of the body. It would also explain the convulsions. It is not clear from the record whether the blood pressure was elevated during these seizures. That would be an important point. I am given the admission blood pressure and the blood pressure toward the end of the illness. If the blood pressure was elevated at the time of the convulsions it would explain this occurrence.

There are some formidable obstacles to a diagnosis of glomerulonephritis, however. In the first place, I have never seen a patient with glomerulonephritis who had hypertensive encephalopathy with normal eye grounds. We are repeatedly reminded that the eye grounds were normal.

DR. WINFIELD S. MORGAN: At the time of the convulsions, the blood pressure was 160 systolic, 100 diastolic.

DR. KRANES: That is somewhat high but not enough, I should think, to precipitate an attack of hypertensive encephalopathy. Moreover, the normal ocular fundi lead me to believe this may not have been an attack of hypertensive encephalopathy.

The second consideration is the anemia. Patients with renal insufficiency have some degree of anemia, but this was unusually severe. It is quite rare for a hemoglobin to drop to a level of 2.6 gm. in renal insufficiency in the absence of gross blood loss. Certainly, any blood loss that would have reduced the hemoglobin to that level should have been quite evident. Furthermore, this appears to have been a hemolytic anemia, because in spite of repeated transfusions, the hemoglobin dropped. It is usually a simple matter to raise the hemoglobin level by transfusions in patients with anemia. It therefore appears that the hemolytic process involved not only the patient's cells but also the cells of the donor. I should like more data about the anemia. I should like to know what the reticulocyte count was; apparently, it was high because stippled cells were noted in the peripheral blood. I should also like to know about the urobilinogen excretion.

The third obstacle to a diagnosis of glomerulonephritis is the development of thrombopenic purpura. Hemolytic anemia and thrombopenic purpura might, I suppose, complicate any chronic disease, but in that case I should have to make additional diagnoses.

I must therefore explore other fields. The moment I do this, however, I leave firm ground for the realm of the unusual diseases and syndromes — I leave the dandelions and roam among the orchids, or, as Dr. Howard B. Sprague more aptly puts it, one must reach into the back of the textbook.

I should first ask what diseases affect the salivary glands and also involve the kidneys. There are several. Sarcoidosis? Having made the statement, I find it difficult to go any farther with it. Sarcoidosis is known to produce renal lesions but rarely to any extensive degree. Although it is true that some people with sarcoidosis have renal insufficiency, the cause of the renal insufficiency has never been evident since most of the patients have recovered. Renal insufficiency with sarcoidosis is likely to be associated with hypercalcemia; so that the renal disease is probably nephrocalcinosis. It is by no means proved. Massive involvement of both kidneys by this granulomatous process is extremely rare. Furthermore, if I make the diagnosis of sarcoidosis, I have to explain the hemolytic anemia and thrombopenic purpura. Although there have been a few cases of sarcoidosis in which thrombopenic purpura has been reported as a complication, I do not like to invoke several different diseases if I can possibly avoid it.

Another disease that affects both systems is primary systemic amyloidosis. This diagnosis appeals to me, and I should like to make it but find myself unable to do so for almost the same reasons that apply to sarcoidosis. Amyloidosis does involve the kidneys, to be sure, but it does not usually produce hematuria, unless I assume that the hematuria was the result of the thrombopenic purpura. And again we come up against the hemolytic anemia — at least I think it was hemolytic; there was no evidence to the contrary. No Congored test was done, but with primary systemic amyloidosis, this test might have been negative.

Leukemia is another disease that involves both sets of organs. Many features of this case might be explained by a diagnosis of leukemia. Certainly, the thrombopenic purpura and the severe degree of anemia might. Hemolytic anemia occasionally complicates leukemia, but I have never yet encountered a patient with leukemia who had this degree of renal insufficiency. Leukemia results in infiltration of the kidneys but not to the degree that would produce renal insufficiency. Furthermore, if this patient had leukemia of sufficient magnitude to cause infiltration of the salivary gland, I should have expected it to be evident if not in the peripheral blood, at least in the bone marrow. Yet in all smears no abnormal cells were found. Since my efforts to explain the renal disease and Mikulicz's syndrome on a single basis have not been very successful, I must go still farther afield.

Here one thinks immediately of the group of diseases that we might term vasculitis, diffuse small-vessel involvement. Outstanding among them is polyarteritis nodosa. Many features of this patient's story would fit such a diagnosis. It would explain the hematuria, the renal insufficiency, the gradually rising blood pressure, the fever, the skin lesions and so on. Polyarteritis has the additional virtue of explaining the central-nervous-system symptoms, which some of the other suggested diagnoses did not. But the hemolytic anemia and the thrombopenic purpura as complicating factors are

again a stumbling block. Could the patient have had lupus erythematosus? She was a woman and had renal disease, and the white-cell count was low. Convulsions have been described with lupus; they are not too infrequent in the terminal stages of lupus. The same objections, however, apply to lupus that apply to polyarteritis nodosa. Another diffuse vascular disease, diffuse platelet thrombosis or thrombotic thrombocytopenic purpura,[1] could also explain most of the features in this case. It is one that I hesitate to suggest because of its rarity, but it deserves some consideration. It is a disease in which the capillaries and precapillary arterioles become plugged with a hyaline mass. This hyaline mass is thought by many pathologists to be agglutinated platelets, but that has by no means been established. The disease involves many of the organs of the body, especially the kidneys, the pancreas, the central nervous system and so on. This disease, of unknown etiology, is thought by some physicians to be related to lupus erythematosus,[2] but here again there is wide disagreement. As a matter of fact, the description given here is practically the classic or textbook description of thrombotic thrombocytopenic purpura, if one is permitted to use that phrase about a disease of which there are only 40 or 50 recorded cases. It is characterized clinically by fever, thrombopenic purpura, hemolytic anemia and transient neurologic disturbances, all of which were found in the case under discussion. The majority of patients have hematuria. Many of them have renal insufficiency. Occasionally, this disease is a terminal phase in another more chronic disease, and perhaps that may have been the case here.

Now, having discussed all these possibilities, I have to make up my mind. I cannot connect the salivary-gland enlargement with the renal disease, and I am forced to make two separate diagnoses. What involved the salivary glands, I shall not attempt to say except to call it Mikulicz's syndrome. Of the other diseases, it seems to me the syndrome of thrombotic thrombocytopenic purpura best explains the facts given here. That may not be the correct diagnosis, but it seems to me the most logical one. I hesitate to mention it because of its rarity, but heretofore that has not been a serious objection at a clinicopathological conference.

DR. MADAN M. SINGH: In a recent report 34 cases of disseminated lupus were reviewed[3]; 3 of the patients had enlarged parotid glands, 1 had parotitis for five years and was admitted to the hospital with the chief complaint of parotitis. About a third had thrombocytopenia, and some had acquired hemolytic anemia.

DR. KRANES: How many had enlarged salivary glands?

DR. SINGH: Three patients out of 34.

DR. KRANES: I did not know that could be a complication of lupus.

DR. SINGH: The authors found no report of this complication of lupus in the literature.

DR. KRANES: It is perfectly possible that this patient had lupus, but I shall still vote against it.

DR. WILLIAM H. BAKER: What about lymphoma?

DR. KRANES: Lymphoma should always be mentioned in any bizarre syndrome. The same objections can be raised to lymphoma, however, as were raised to other lesions that involve the salivary glands; in addition it is hard to explain the renal insufficiency on the basis of lymphoma. The anemia is readily explainable but the thrombopenic purpura would have to have been a second disease.

DR. BAKER: Diffuse involvement of the kidneys occurs.

DR. KRANES: Enough to produce renal insufficiency?

DR. BAKER: Yes.

DR. BERNARD M. JACOBSON: I wish we had had as much imagination at the time the patient was alive as Dr. Kranes has. Thrombotic thrombocytopenic purpura is a very interesting thought, which I must admit two years ago never occurred to us. Two additions that make it hard for me to accept that diagnosis are that when she came into the hospital, the platelets were normal, and before the rapidly developing renal insufficiency, she did not have purpura or thrombopenia.

DR. KRANES: Those are not serious objections. These patients may have perfectly normal platelets in the early stages of the disease and then develop thrombopenia. As a matter of fact some never develop thrombopenia.

DR. JACOBSON: If they do not, one cannot make the diagnosis during life.

DR. KRANES: No; but the pathologists tell us the patients had the disease.

DR. JACOBSON: With respect to the hemolytic anemia, the last hemoglobin of 2.6 gm. the day before death could be explained by the very active bleeding from the uterus during the last week of her illness. As late as the third week of illness, the platelets were 350,000 when the hemoglobin was 11.8 gm. I do not see that information in the history.

DR. KRANES: That information is quite illuminating.

DR. MORGAN: I am not able to find the report of that count in the record.

DR. KRANES: Do you think the patient bled enough to reduce the hemoglobin to the level of 2.6 gm.?

DR. JACOBSON: Terminally, yes; but she had not bled enough to reduce it to 5 gm. eleven or twelve days before death. I do not doubt that she had some hemolytic process, — many of these patients do, — but it was not a frank hemolytic anemia.

DR. KRANES: Why was the hemoglobin not increased by transfusions if she was not losing red cells? She apparently received many.

DR. JACOBSON: She was losing blood in the kidneys.

DR. KRANES: A patient does not lose that much with 50 to 100 red cells per high-power field! How many transfusions did the patient receive?

DR. JACOBSON: There were quite a number.

DR. KRANES: That the hemoglobin continued to go down was the reason I assumed that she had hemolytic anemia.

DR. MORGAN: Dr. Palmer, you saw this patient; would you tell us your opinion?

DR. ROBERT S. PALMER: At the time I saw her I thought she might have acute glomerulonephritis with an associated acute vasculitis, diffuse in extent and apparently intense in progress, involving the kidneys and the brain; elevation of the blood pressure was not apparent when she was first observed. In glomerulonephritis there may be cerebral symptoms with very little or really no elevation of the blood pressure.

DR. KRANES: And with normal eye grounds?

DR. PALMER: No; not with normal eye grounds. The patient had vitreous hemorrhages. It was soon clear that she was dying in uremia and that the blood was being destroyed rapidly by whatever destroys the blood in a person who has uremia. I concluded that this was the rapidly progressing terminal stage of one of the strange diseases, probably one of the group diseases.

CLINICAL DIAGNOSES

Renal insufficiency, cause unknown.
Mikulicz's syndrome, cause unknown.

DR. ALFRED KRANES' DIAGNOSES

Thrombotic thrombocytopenic purpura.
Mikulicz's syndrome of salivary glands.

ANATOMICAL DIAGNOSES

Lupus erythematosus, with involvement of kidneys.
Mikulicz's disease of salivary glands.

PATHOLOGICAL DISCUSSION

DR. MORGAN: At autopsy the peritoneal and pleural cavities contained a small quantity of clear serous fluid and a few adhesions. The lungs were slightly congested, and the heart was normal except for a minimal fibrinous pericarditis. The kidneys were normal in size, weighing 350 gm. together, and had finely granular cortical surfaces, with a few scattered petechial hemorrhages.

Microscopically, the significant findings in the general examination were confined to the kidneys, which revealed hyaline thickening of the capillary walls of the glomeruli, with the formation of wire-loop lesions characteristic of lupus erythematosus. The bone marrow showed a hyperplasia of the red-cell elements and very few megakaryocytes or cells of the white-cell series. In the left frontal lobe there was an area of old infarction that probably explains the seizures forty-seven days before the patient died. In addition there were diffuse nonspecific changes in the brain consistent with the toxic state.

The salivary glands were of particular interest to us, and this case is 1 of 18 cases of so-called Mikulicz's disease that we have just finished studying.[4] In this group of cases there was wide variation in involvement of the glands, some cases being bilateral and others unilateral; yet all revealed the same pathologic process microscopically. Follow-up study for as long as sixteen years after excision of the diseased gland indicated that the disease was benign. A majority of the patients in this series were middle-aged women. Microscopically these glands revealed progressive atrophy of the acinar parenchyma, with replacement by lymphoid tissue. Associated with this, and occurring concomitantly, is a characteristic change in the ducts. This consists of an intraductal proliferation of epithelial and myoepithelial cells leading to obliteration of duct lumens and the formation of solid masses of cells that we have come to call "epimyoepithelial islands." On the basis of these duct changes this condition can easily be differentiated from malignant lymphoma.

In a review of the literature on this subject a series of articles by Sjögren[5] was encountered in which he described a syndrome, which was chronic and occurred usually in middle-aged women, one component of which was enlargement of the salivary glands. Sjögren's syndrome, well known to ophthalmologists, consists of a dry keratoconjunctivitis, dryness and atrophy of the mucous membranes of the nose, mouth, pharynx and larynx, enlarged salivary glands and rheumatoid arthritis. We obtained permission to review Sjögren's original slide material of the salivary glands in his series, and found in every case the same pathologic process microscopically as described in our 18 cases previously considered to be Mikulicz's disease.

A clinical review of our cases disclosed that 3 patients had keratoconjunctivitis sicca, 5 had rheumatoid arthritis, 1 — the case discussed today— had lupus erythematosus, and 1, a fifteen-year-old boy, had had rheumatic fever several years before and had continued to have an elevated sedimentation rate up to the time he entered the hospital because of an enlarged salivary gland.

Therefore, we believe that, from the standpoints of clinical course, sex and age incidence, the disease in the salivary and lacrimal glands and the presence of certain associated conditions, our 18 cases previously interpreted as Mikulicz's disease and cases of Sjögren's syndrome cannot be distinguished. Since we were unable to find any other pathologic process of those glands that would better fit the original description by Mikulicz, it is possible that what in the past has been called Mikulicz's disease is not a separate clinical and pathological entity but merely a variant of Sjögren's syndrome in

which enlargement of the salivary or lacrimal glands is the most prominent feature. It is even possible that these cases are related etiologically to rheumatoid arthritis, although one does not usually think of epithelial changes, such as were found in the ducts, in the so-called collagen-group diseases.

In the article[3] referred to by Dr. Singh in which 34 cases of lupus erythematosus were reviewed, 3 patients were said to have had chronic, nonsuppurative parotitis. This was bilateral in 2 and unilateral in the other. The parotid glands were described as enlarged, firm and tender. Interestingly enough, 1 of these patients had had glandular enlargement for five years and entered the hospital, as did the patient under discussion, with the chief complaint of parotid swelling. The observation that in these 3 cases the parotitis was chronic suggests that the pathologic process in the salivary glands may have been the same as that found in our series. Unfortunately, no definite statement about this can be made since the parotid glands were not removed in any of these 3 cases at time of autopsy.

DR. KRANES: Microscopical examination of the tissues was negative except for the kidneys?

DR. MORGAN: In this particular case there was no other microscopical evidence of lupus. There was the polyserositis.

DR. KRANES: On what findings in the kidneys did you base the diagnosis of disseminated lupus?

DR. MORGAN: On the wire-loop changes.

DR. HEATH: Were the lacrimal glands involved?

DR. MORGAN: Unfortunately, the lacrimal glands were not removed.

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CASE 39192

PRESENTATION OF CASE

An eighty-two-year-old man was admitted to the hospital because of episodes of upper abdominal pain.

The patient was well until seven months before admission, when he noted the gradual onset of aching in the left upper quadrant. This did not radiate, but was associated with gas and belching and came in episodes lasting about a day and then subsiding for a similar period. It tended to be more severe and to take on a knife-like character when the patient ate large meals, and was alleviated by small meals. There was no nausea, vomiting, hematemesis, melena or change in bowel habits. Two months later, when the patient was seen in the Out-Patient Department, examination did not show lymphadenopathy and the abdomen was soft, with slight epigastric tenderness. The liver edge was palpated 1 or 2 fingerbreadths below the right costal margin. No masses were felt. The blood hemoglobin was 12.4 gm., and a gastrointestinal series showed the stomach to be displaced upward and laterally to the left, with no peristalsis in the lesser-curvature portion of the stomach (Fig. 1). A roentgenogram of the chest was normal. A low-residue diet was prescribed, and on this the patient became free of discomfort. Ten days before admission he began to have tarry stools three or four times a day with a sensation of urgency. Several days later the drinking of eggnog or coffee brought on pain in the left upper quadrant and vomiting of ingested fluid. His stools continued to be black, and he came to the hospital. He stated that throughout his illness, except for the last week when weakness supervened, he had felt well and had had a fair appetite. There had been no weight loss.

Physical examination revealed a thin, pale man in no distress. There was no jaundice. The chest was clear, and the heart was normal except for a soft, blowing apical systolic murmur. There were no palpable masses or organs in the abdomen, and there was no tenderness.

The temperature was 99.5°F., the pulse 85, and the respirations 24. The blood pressure was 118 systolic, 75 diastolic.

The urine was normal. Examination of the blood showed a hemoglobin of 7.5 gm. per 100 cc. and a white-cell count of 8700, with 71 per cent neutrophils, 20 per cent lymphocytes, 7 per cent monocytes and 2 per cent basophils. The serum nonprotein nitrogen was 35 mg., and the total protein 6.3 gm. per 100 cc., and the chloride 106 milliequiv. per liter. The prothrombin time was normal. Several stool specimens were brown and guaiac negative. On gastric aspiration 50 cc. of clear, guaiac-negative fluid was recovered.

On a gastrointestinal series the esophagus was normal. There was a filling defect measuring approximately 3 cm. in greatest diameter in the

posterior aspect of the cardia of the stomach, displacing the distal end of the esophagus superiorly. The lesser curvature was somewhat stretched, suggesting extrinsic pressure in this region. No abnormality was demonstrated in the distal portion of the stomach; the duodenal cap and loops and the visualized upper small bowel were normal.

The patient was given transfusions, and on the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Earle Wilkins*: From the protocol this man could have had any one of several diseases. Since I did not come prepared with a final diagnosis, I shall have to rely heavily on the x-ray films. May I see them now?

Dr. Joseph Hanelin: There were two examinations, done five months apart, which show the same finding, and any apparent difference might easily be attributed to a different degree of distention of the stomach by barium. There is evidence of a mass adjacent to the lesser curvature of the stomach from the fundus to the angle. It has displaced the stomach to the left and anteriorly (Fig. 1). The finding is essentially the same five months later, but the stomach contains more barium at that time. This mass may have arisen from the stomach or from some adjacent structure and become adherent to it. I do not see any actual ulceration of the stomach; there was questionable peristalsis.

Dr. Wilkins: Was there no peristalsis on the second examination either?

Dr. Hanelin: No peristalsis was reported although there is some rippling along the lesser curvature in the second films, suggesting that this curvature is not completely rigid.

Dr. Wilkins: What does the statement that the lower end of the esophagus was displaced superiorly mean?

Dr. Hanelin: I think it must refer to a finding that was present on all films — namely, that the diaphragmatic portion of the esophagus is displaced anteriorly to an abnormal degree before entering the stomach.

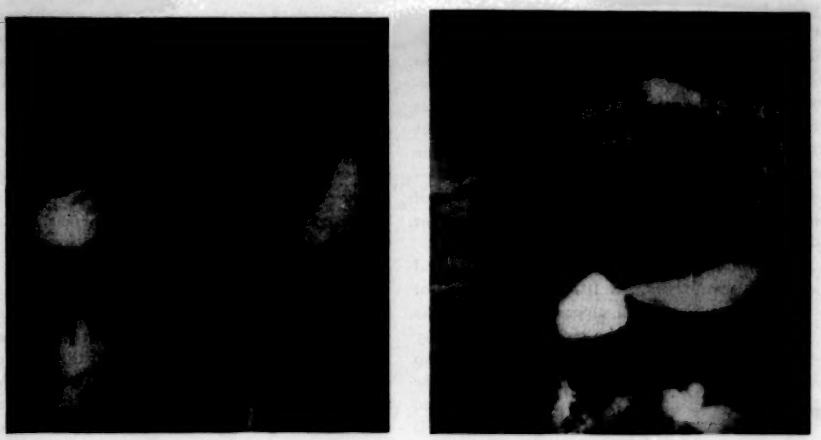

Figure 1. *Posteroanterior and Right Anterior Oblique Views, Showing Pressure Deformity on the Posterior Aspect and Lesser Curvature of the Stomach.*

Dr. Wilkins: Certainly, any man of eighty-two who has had vague upper abdominal symptoms that seem to be gastric in origin should be considered to have a carcinoma of the stomach until the contrary is proved. There was a period of about seven months between the time of onset of symptoms and the time he came into the hospital, which would favor carcinoma. Dr. Arthur W. Allen and Dr. Claude E. Welch, who have gone over all the carcinomas of the stomach in this hospital, have

*Assistant in surgery, Massachusetts General Hospital.

found now, as compared with ten, twenty and thirty years ago, that the length of time from the onset of the symptoms to entry to the hospital has remained the same, about five months. Certain things about the initial symptoms, including pain on eating of large meals, might suggest an infiltrating lesion along the lesser curvature that caused pain on distention of the stomach. I might go so far as to explain the relief of the pain by small meals on the basis of a superficial ulceration. The symptoms of pain on eating or drinking that this patient had a few days before admission, followed by vomiting of the ingested material, suggest that the lesion that Dr. Hanelin has demonstrated obstructed the proximal portion of the stomach or the cardia. When the patient was seen in the Out-Patient Department five months before entry, the liver was slightly enlarged, but since on admission to the hospital it was not felt I shall dismiss it as being normal. No masses were palpated at either time. I cannot explain why the initial symptoms, from which he was free from the time he was seen in the Out-Patient Department until ten days before entry, were completely relieved by a low-residue diet. It is difficult to believe that a man with carcinoma of the stomach would be completely free of symptoms during this interval.

The hemoglobin was 12.2 gm. and on the second admission was 7.5 gm. per 100 cc.; on the basis of the symptom of melena, I suppose that most of the blood loss took place in the ten days before entry and that the hemoglobin did not necessarily drop slowly over the period of five months. Then the patient had bleeding, which we have all come to believe is not as common with carcinoma as it is with certain other lesions of the stomach. This was apparently slow oozing of blood because he never vomited. His blood pressure was normal when he came in, and he was not in shock. Massive bleeding with carcinoma of the stomach is usually a late manifestation, and when it occurs the diagnosis can usually be made on the basis of symptoms and x-ray findings without the need for further study. Apparently, this man did not fall into that category because he felt well, had a fair appetite and had not lost weight; except for the weakness, which I can attribute to anemia, he was apparently in good shape. The physical examination does not contribute much except in a negative way.

The laboratory data except for the anemia are not very helpful. It is interesting that the stool specimen was brown and guaiac negative when the patient came into the hospital although he had been passing blood for several days. I wonder whether the acidity of the fluid obtained on gastric aspiration was determined or whether it was studied in the Cytology Laboratory.

I suppose the physicians who saw the patient five months before entry thought that at his age he was in too good health to be sent into the hospital, but I think any man presenting an abnormality in the gastrointestinal films certainly should have been admitted to the hospital for further study.

All these little inconsistencies together tend to make me believe that this was probably not a straightforward carcinoma of the stomach although statistically that is the most likely condition. What are the other possibilities? This could have been a lymphoma, but the same inconsistencies apply. Lymphoma may produce massive bleeding as one of the presenting symptoms, but there was no evidence of lymphadenopathy; the chest films were reported as normal, and the patient had no fever, malaise or any of the other symptoms that go with lymphoma. However, malignant lymphoma limited to the stomach does occur.

A benign tumor of the stomach is a possibility — I assume that the tumor was actually in the stomach because there were gastric symptoms and hemorrhage and a mass noted in the gastrointestinal series. Many of the mesenchymal tumors of the stomach can cause hemorrhage, and many of them present with massive hemorrhage; they include the leiomyoma group, the fibromas, the neurogenic tumors, even lipomas and certain vascular tumors. To choose from that group would be guesswork. I suppose that the most likely would be a leiomyoma or a leiomyosarcoma. Palmer,[1] who wrote a review article on the subject of benign tumors, found about 610 cases reported in the literature; these benign tumors occurred at any age between nine and ninety-four so although this man was eighty-two and one might postulate that he was rather old for this diagnosis, such a possibility is not unheard of. The tumors occur at any level of the stomach; they may be intramural and project inwardly, or may grow out serosally like a fibroid in the uterus. They do not usually present symptoms until they

are fairly large and cause pressure or until they ulcerate and give evidence of bleeding. Meissner[2, 3] has made the statement that the leiomyomas are the most common tumors of the stomach. He includes all the small tumors that are not symptomatic. In 50 consecutive autopsies 23 stomachs, or 46 per cent, contained leiomyomas.

Could this have been some other lesion that caused gastric bleeding? I am not going to consider any of the others, which include benign ulcer, hiatus hernia, gastritis and even aneurysm of the stomach wall.

Although statistically I should expect that the most likely diagnosis is carcinoma, I am inclined to stick my neck out and make the diagnosis of leiomyoma.

DR. PERRY J. CULVER: I should like to ask Dr. Wilkins why this might not have been a cystic lesion of some sort since it changed shape with the increased filling of the stomach. What does he think of the possibility of a small ulcer that perforated into the lesser omental cavity and produced an abscess in that area?

DR. WILKINS: The radiologist interpreted the gastric mucosa as being intact, without evidence of ulceration.

CLINICAL DIAGNOSIS

Benign tumor of stomach, with ulceration.
?Carcinoma of stomach.

DR. EARLE WILKINS' DIAGNOSIS

Leiomyoma of stomach.

ANATOMICAL DIAGNOSIS

Leiomyoma of stomach.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Dr. Shannon, you operated on this patient; would you tell us the opinion preoperatively?

DR. JAMES M. SHANNON: We thought this was probably a benign tumor and explored the patient through a left thoracoabdominal incision. We found a freely movable mass, 10 by 10-cm., on the lesser curvature of the stomach in the region of the left gastric vessels; it was readily removed by a sleeve resection of the stomach, and the distal and proximal segments of the stomach were anastomosed. The mass presented about 6 cm. from the esophagogastric junction and was attached to the lesser curvature in the gastrohepatic ligament. There were no enlarged lymph nodes, and it was believed to be a benign tumor.

DR. MORGAN: The specimen that was received in the laboratory was nodular, firm and roughly spherical; it measured about 10 cm. in diameter. Attached to one surface of the mass was a circular piece of gastric mucosa in the center of which was a small dimpled area. Microscopically, the tumor proved to be a typical leiomyoma, consisting of interlacing bundles of smooth muscle, and showed numerous areas of necrosis. A section through the dimpled area in the mucosa confirmed the gross impression that that had been the site of an old ulceration, which was no longer active.

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A HOSPITAL PUBLIC-RELATIONS OFFICER

YEARS of experience in private and hospital practice will manifest to the physician that an important and often neglected phase of the work of the hospital, or hospitals, with which he is most intimately acquainted is the matter of all-round public relations. As a rule, newspaper publicity is good, and neat and expensive brochures are often used to inform the residents of the community of the various technical advantages that the hospital offers. This is excellent, as far as it goes. Expert social workers are often able, when time allows, to translate the medical needs of the patient into terms of practical adjustment to life after discharge from the hospital. Nevertheless, among the group of patients of practically every hospital there are those who have been offended, those who think that they have been badly treated, those who have not understood their own problems and those who are sure they would never willingly return.

Compared to the well satisfied and grateful patients, this group is usually small and contains many persons in whom a paranoid trend is evident; yet it is often a voluble group, able and willing to do the hospital a great deal of harm. It is with the attempt to prevent this resentment and to do away, as far as possible, with the circumstances that cause it that one is primarily concerned. It must regretfully be admitted that such causes exist, at times, even in the best regulated hospitals.

An example is provided by the patient who, after arriving sick and frightened and often suffering considerable pain, is allowed to lie for an hour or two on a stretcher in an admitting room because the admitting physician is attending someone else. Such experiences are not often forgotten, and they occur every day. Another is the impressionable person who is permitted to overhear remarks about his condition that frighten him, or who is unjustly criticized by a brusque orderly, nurse or physician for being "unco-operative," when in reality he is merely confused and quite ignorant how he should act. Then, at times, one finds members of a family deeply resentful because an aged parent is treated disrespectfully, unkindly or even awkwardly or roughly by hospital personnel or incensed because operative or other important procedures are undertaken without notification to them of the time or the significance of what is being done. These are just a few of the situations that occur too frequently and undermine the hospital's community support.

Besides patients and their families, there is a group whose reaction to the hospital is important and by no means always favorable — the general practitioners whose patients are referred to the hospital but who are not themselves staff members. Courtesy to these physicians, consideration of their opinions and scrupulous care in the return of their patients to them, with clear and concise summaries of the hospital records, is the policy of most hospitals. Too often this policy is not carried out, and the practitioner is left dissatisfied or disgusted.

A third group of people, who are often keen and critical observers of the personal side of patient care in hospitals, includes the volunteer workers. Under no financial obligation whatsoever to the hospital, they often feel free to talk about it as they choose, and they are not invariably understanding.

There is no propaganda possible for the creation of an atmosphere in a community favorable to the continued support of its hospital to compare with that created by grateful and loyal patients and satisfied community physicians. It may also be added that in many clinical conditions what is said to a patient may be more important than what is done for him — a fact that every practitioner knows. In many cases, as a result of tactless or misleading remarks, the value of hospital treatment is lost — submerged by feelings of hostility, resentment or unfounded apprehension.

This problem is reasonably well understood by hospital administration, but the steps taken to correct the situation have, as a rule, been relatively ineffective. They include instructions to house staff and visiting staff, formally in meetings and conferences, and informally on ward rounds. Another method, which is perhaps well worthy of consideration, is the appointment of a full-time public-relations officer, who should be, if possible, an experienced practitioner, preferably a consultant, former member of the active staff or retired chief of service, who both personally and professionally has the confidence and respect of the staff. Such a man could make it his business to see all dissatisfied or confused patients and their families, interpret clinical situations to them and help them make decisions. He would be alert to follow up any evidence of neglect or unkindness on the part of hospital personnel toward patients and to instruct such personnel in proper deportment. He would work hand-in-hand with social service. He would also maintain close touch with all volunteers, whom he would indoctrinate and instruct, and whose aid he might at times request. He would extend all possible courtesies to practitioners who send in patients including the suggestion that they make visits to the hospital and its clinical conferences, and would see to it that proper reports of the patient's hospital stay reached the family doctor along with the patients themselves. He would also have general charge, under the supervision of the director of the hospital and the board of trustees, of all other aspects of public relations. Such an officer should be paid an adequate salary, for it is clear, in both civilian and governmental hospitals, that, if the right person were selected for this position, he would save the hospital many times the expense of his salary.

TWELFTH CONFERENCE ON CHEMOTHERAPY OF TUBERCULOSIS

The conferences on the chemotherapy of tuberculosis, first semiannual and now annual, under the sponsorship of the Veterans Administration have contributed and crystallized numerous outstanding advances in the field of tuberculosis therapy. They have not only stimulated interest and enthusiasm among the members of the staffs of the participating Veterans Administration, Army and Navy hospitals for tuberculosis but also instilled in the physicians of those hospitals a spirit of genuine inquisitiveness, objectivity and progressiveness — a far cry from the frequently remote and cloistered existence of the phthisiologists in most tuberculosis sanatoriums.

The twelfth and most recent of these conferences, which was held in Atlanta in February, proved to be fully as lively and stimulating as any of its predecessors. The keynote was struck in the introductory paper by Dr. William B. Tucker, of Minneapolis, one of the guiding spirits of the meetings. In a historical review he traced the careful and laborious manner in which the collaborating hospitals have gone about systematically obtaining definitive answers to important specific questions dealing with the efficacy, drawbacks and comparative values of successive regimens. They have accomplished this by mapping well-thought-out programs, applying them to cases selected strictly at random, collecting and recording essential data on well designed and practical forms and, finally, employing acceptable objective statistical analysis to the data thus collected. He also reviewed the many pilot studies, designed to give quick answers to specific questions, that have offered the greatest opportunity for the exercise of initiative, imagination and skill and have

led to adoption of basic regimens subsequently studied by all the collaborating groups. Much progress has been made, and useful information gathered in this manner. Conclusions arrived at by such methods can be relied upon as being sound and are most apt to stand the test of time.

In another review paper Dr. James D. Murphy, of Oteen, North Carolina, traced the changing trends in the surgery of tuberculosis, away from the extensive, mutilating surgical procedures toward the increasing use of segmental resections of stabilized lesions with the preservation of maximum amounts of healthy lung. These changes have recently been made more feasible and the results more successful by the proper application of optimum chemotherapeutic regimens worked out in the conferences.

Some of the more detailed discussions concerned data on the comparative efficacy of isoniazid used alone or in combination with either streptomycin or para-aminosalicylic acid or both. Statistics on clinical and laboratory effects under various conditions were collected, and the effect of the use of the different combinations on the emergence of resistance to each of the drugs was also studied. The importance of using isoniazid in combination with other effective antituberculosis drugs was stressed. Among other features it was brought out that the combination of isoniazid and streptomycin delayed, but did not prevent, the emergence of tubercle bacilli resistant to both agents. In this respect the combination of isoniazid and streptomycin was considered to be inferior to that of streptomycin and para-aminosalicylic acid.

One of the most interesting and heated discussions dealt with the important question of whether tubercle bacilli seen in resected lesions after prolonged chemotherapy are actually viable. Most of these organisms cannot be cultivated and do not produce lesions in susceptible animals. Obviously, if there are no viable organisms left in the lungs of the patient after prolonged chemotherapy, the need for resections of residual lesions must be re-examined.

There were also papers dealing with comparisons of streptomycin and dihydrostreptomycin; the mechanism of action and the pharmacology of isoniazid; the virulence of isoniazid-resistant organisms obtained from patients, or developed in vitro; and the therapy of genitourinary, miliary and meningeal tuberculosis and the contribution of isoniazid in these types — and many others. Looking ahead, the conference explored plans for careful re-examination of some of the more basic aspects of the management of patients with tuberculosis.

All the deliberations will, of course, appear in *Transactions*, which necessarily have limited distribution. Many individual papers — perhaps most of them — will eventually find their way into the general medical literature. It is to be hoped that the reviews by Tucker and Murphy will soon be made available in an accessible journal together with a summary of the more significant and practical conclusions arrived at in this conference.

The Veterans Administration and the workers in its tuberculosis division responsible for arranging these conferences are to be congratulated on this highly successful effort. It is hoped that the means will be provided for continuing the conferences and maintaining their high standard of performance.

"PLACE 'MID THE BARDS"

Achievements by doctors in fields unrelated to their profession are no longer a source of surprise to their less versatile medical brethren or their patients: literary and artistic proficiency has come to be accepted as a frequent accompaniment of scientific capacity. Periodically, under the heading "Doctors Afield," in the department of Medical Intelligence, the *Journal* has cited and paid tribute to what may be considered the extracurricular activities of men of medical science — both those who, like Oliver Goldsmith and Friedrich Schiller, were failures as physicians and those such as Leonard Wood and Albert Schweitzer whose contribution to medicine has been outstanding.

A place of great honor among such attainments is held by the tradition, typical of but by no means confined to Boston, of the physician learned and accomplished in the classics. His love of the ancient forms and the languages he can never regard as dead is matched by the zeal that prompts him to help keep the literature of the pre-Christian era from neglect. He is distinguished, not only among his medical colleagues but also among educated men in general, by his efforts to preserve for more than a happy few the lore of antiquity.

The forthcoming publication of a selection of the works of Horace,* translated into English by Dr. Robert M. Green and the late Dr. Fred B. Lund, is therefore welcomed with the keenest interest, both for its own sake and as yet another milestone in the progress of the doctor afield — but not divorced — from his specialty. This work, which will be published by the Club of Odd Volumes next autumn if sufficient subscriptions are received, contains twenty-eight translations by Dr. Green and forty-eight by Dr. Lund. The lines of the great Roman poet are interpreted in English verse of rare felicity and grace but with scrupulous fidelity to the content and spirit of the original. Lovers of the classics can be grateful to the Club of Odd Volumes for making the translations available.

The book may be obtained only by subscription. Mr. Walter Muir Whitehill, Clerk, Boston Athenaeum, 10½ Beacon Street, Boston, will accept subscriptions until June 1, 1953. He will also, on request, furnish information regarding the details of publication. It is confidently expected that physicians, especially in the Boston area, will submit sufficient subscriptions to make publication possible.

*Quintus Horatius Flaccus: *A selection of his works rendered into English verse by two Boston physicians: Fred Bates Lund, M.D., and Robert Montraville Green, M.D. With an Introductory Essay by Peter Oliver.* 144 pp. Boston: Club of Odd Volumes, 1953.

VITAL STATISTICS

The year 1952 marked another bold step toward the millennium, especially for that happy group of favored mortals, the industrial policyholders of the Metropolitan Life Insurance Company. For their average length of life and that of their families had increased to sixty-eight and a half years and their death rate from tuberculosis had dropped to a new low of 13.5 per 100,000 insured, compared with a figure for the population as a whole that was estimated at a little under 18.

Other record lows were recorded for policyholders: in deaths from the complications of pregnancy and childbirth and in those from pneumonia and influenza and the principal communicable diseases of childhood, all of which equaled their previous all-time lows. This, however, was not unexpected, for it is in these categories that the greatest gains have been and are still being made.

The exciting feature of the report is that the death rate has also declined for each of the major chronic diseases of middle and later life — that from the degenerative diseases of the cardiovascular system and kidneys by nearly 2 per cent. For cancer and allied conditions the rate declined from 123.5 per 100,000 in 1951 to 122.5 in 1952, and for diabetes from 15.2 to 14.0.

The death rate from accidents, on the other hand, relatively unchanged for the general population, showed an increase of 9 per cent for policyholders. This was largely attributable to an increase in motor-vehicle fatalities.

It should be safe to assume that if these trends continue year by year to their logical conclusion, with so-called natural deaths declining to their vanishing point, all persons will eventually die as a result of accident. Death will thus be reduced from its present status as an inevitable termination of existence, usually from natural causes, to that of an accidental phenomenon. Stated more simply, death by accident would then become natural, and natural death, if it ever occurred, would be accidental.

Being brave behind a high wall, and facing the guns of an enemy, are conditions widely different.
Boston M. & S. J., *May 11, 1853*

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council of the Massachusetts Medical Society will be held in the Georgian Room, Hotel Statler, Boston, on Monday, May 18, 1953, at 7:00 p.m.

Business:

Call to order at 7:00 p.m.

Presentation of record of meeting held February 4, 1953, as published in *The New England Journal of Medicine*, Supp. No. 1, Vol. 248, March 26, 1953.

Reports of standing and special committees.

Such other business as may legally come before this meeting.

Robert W. Buck, M.D.
Secretary pro tempore

The *Journal* lacks extra copies of January 22, January 29, February 5 and February 19, 1953, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Low Fat Diet Cook Book. By Dorothy Myers Hildreth and Eugene A. Hildreth, M.D. With an introduction by Francis C. Wood, M.D. 8°, cloth, 148 pp. New York: Medical Research Press, 1952. $2.95. (Distributed by Grosset and Dunlap.)

Mrs. Hildreth, in conjunction with her husband, has written this small book on the low-fat diet to meet the evidence that fatty foods may play a part in the development of arteriosclerosis.

Disorders in Perception: With particular reference to the phenomena of extinction and displacement. By Morris B. Bender, M.D., professor of clinical neurology, New York University College of Medicine, director, Neurological Service, Bellevue Hospital, and neurologist, the Mount Sinai Hospital, New York City. 8°, cloth, 109 pp., with 5 illustrations and 8 tables. Springfield, Illinois: Charles C Thomas, 1952. $3.00. (Publication No. 120, *American Lecture Series.*)

The author discusses the various aspects of extinction and displacement in relation to perception disorders, under the following heads: modes of stimulation and the phenomenon of extinction, sensory phenomena obtained on simultaneous stimulation in the normal, extinction phenomena in disease, special studies in extinction, extinction and the phenomenon of sensory displacement and the theories of extinction.

Carbohydrate Metabolism: Correlation of physiological, biochemical and clinical aspects. By Samuel Soskin, M.D., director, Medical Research Institute, Michael Reese Hospital, dean, Michael Reese Hospital Postgraduate School, and associate professor of medicine, Northwestern University Medical School; and Rachmiel Levine, M.D., director of metabolic and endocrine research, Michael Reese Hospital, and professional lecturer in physiology, University of Chicago School of Medicine. Revised edition. 8°, cloth, 346 pp., with 75 illustrations and 42 tables. Chicago: University of Chicago Press, 1952. $8.50.

The first edition of this monograph was published in 1946. This second edition has been revised and brought up to date to incorporate the knowledge of the subject gained since 1946. The text is a critical review of the pertinent literature, citing more than 1200 references, which are appended to the various chapters. The publishing is excellent in all ways, and the book is recommended for all libraries as a reference source on the subject.

Applied Physiology. By Samson Wright, M.D., F.R.C.P., John Astor Professor of Physiology, University of London, Middlesex Hospital Medical School. With the collaboration of Montague Maizels, M.D., F.R.C.P., professor of clinical pathology, University of London and University College Hospital Medical School; and John B. Jepson, M.A., B.Sc., D.Phil., A.R.I.C., senior lecturer in biochemistry, Courtauld Institute of Biochemistry, Middlesex Hospital Medical School. Ninth edition. 8°, cloth, 1190 pp., with 688 illustrations. London: Geoffrey Cumberlege, Oxford University Press, 1952. $9.00. (*Oxford Medical Publications.*)

Dr. Wright has issued a new edition of his standard book, last published in 1948. The work, first published in 1926, has had an outstanding record of nine editions and nineteen printings. This new edition is virtually a new book. More than half the text has been rewritten, and the remainder thoroughly revised. The printing was done in Great Britain; the publishing is excellent, and there is an extensive index. The book should be in collections on the subject.

Sex after Forty. By S. A. Lewin, M.D., and John Gilmore, Ph.D. With an introduction by The Reverend Dr. Russell L. Dicks, professor of pastoral care, Duke University. 8°, cloth, 200 pp., with nearly 100 drawings, photographs and photomicrographs. New York, New York: Medical Research Press, 1952. $3.50. Distributed by Grosset & Dunlap.

This small book deals with sexual relations of men and women after the age of forty.

NOTICES

SOUTH END MEDICAL CLUB

The annual hospital meeting of the South End Medical Club will be held at the Free Hospital for Women, Brookline, on May 12 at 12 noon. Dr. A. T. Hertig and his associates on the staff will conduct a clinicopathological conference on an interesting gynecologic case.

AMERICAN NEUROLOGICAL ASSOCIATION

The seventy-eighth annual meeting of the American Neurological Association will be held at the Hotel Claridge, Atlantic City, New Jersey, June 15-17.

SOCIETY MEETINGS AND CONFERENCES

May 12. South End Medical Club. Notice above.

May 18–22. National Tuberculosis Association. Page 664, issue of April 9.

May 19–21. Massachusetts Medical Society. Hotel Statler, Boston.

May 20. Massachusetts School Physicians' Association. Page 663, issue of April 9.

May 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

May 28–31. American Therapeutic Society. Page 746, issue of April 23.

May 30 and 31. Society for Investigative Dermatology, Inc. Page 570, issue of March 26.

June 6. Newer Concepts of Liver Disease. Drs. Franz J. Ingelfinger and Charles S. Davidson. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge. 10:05 a.m.

June 7–9. American College of Cardiology. Page 395, issue of February 26.

June 10–13. American Proctologic Society. Page 746, issue of April 23.

June 15–17. American Neurological Association. Notice above.

June 26–28. American Academy of Dental Medicine. Page 664, issue of April 9.

June 28–July 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

July 8 and 9. Seventh Annual Rocky Mountain Cancer Conference. Page 644, issue of April 9.

August 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

October 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

District Medical Societies

ESSEX NORTH

May 13. Andover Country Club, Shawsheen.

MIDDLESEX EAST

May 13. Annual Meeting. Bear Hill Golf Club. 6:45 p.m.

Calendar of Boston District for the Week Beginning Thursday, May 14

Thursday, May 14

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:30 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.
6:30 p.m. Boston Dispensary. Annual Staff Meeting. Somerset Hotel.

(*Notices concluded on page xv*)